The GMP/GDP Questions & Answers Guide

Version 3.0 of September 2026

About this document

Searching for concrete answers to GMP & GDP questions is a time-consuming activity.

This document is intended to provide a single source of information.

We have summarized GMP & GDP questions and answers from Regulators around the world.

In addition to EMA, FDA, EU, MHRA (UK), and ICH we have also used Q&As from the ECA Academy. The subject index contains some of the "GMP & GDP Key Words" and allows to find Q&As addressing the relevant topic.

It is the intension to update this comprehensive collection and to also add new Q&As once they are available.

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1. EMA (EU)

1.1 Questions and Answers on GMP and GDP

1.1.1 EU GMP guide part I: Basic requirements for medicinal products: Chapter 1: Pharmaceutical quality system

1. What should be the frequency of the product quality review (PQR)?

The product review is expected annually. Review timeframes can be appropriately adjusted based upon manufacturing and campaign duration with adequate justification. The timeframe criteria should be established in a SOP. The trending can include results gathered from the previous period to ensure its robustness. Even if no manufacturing has occurred in the review period, the quality and regulatory review should be conducted as per section 1.10 and include stability results, returns, complaints, recalls, deviations (including those arising from qualification and validation activities) and regulatory background. The review of the last PQR should also be conducted.

1.1.2 EU GMP guide part I: Basic requirements for medicinal products: Chapter 3: Equipment

1. Should metal detectors be used routinely in manufacturing processes for certain dosage forms e.g. tablet compression and encapsulation processes? H+V February 2015

Metal could originate from raw materials as well as from equipment in manufacturing processes where metal parts could generate fragments due to the conditions of operation or damage to the equipment.

It is recommended that metal detection is used for processes prone to this.

In order to avoid routine use of metal detectors the company must demonstrate that it has identified and managed the risks such that the use of metal detectors for that particular process is not needed.

1.1.3 EU GMP guide part I: Basic requirements for medicinal products: Chapter 3: Shared manufacturing facilities

Q1. Are Health-Based Exposure Limits (HBELs) required for all medicinal products?
A: Yes, HBELs should be established for all medicinal products. The toxicological or pharmacological data, on which the HBEL calculation relies, requires periodical re assessment throughout a product's lifecycle.

Q2. Is there a framework that could be used to define the significance of the Health-Based Exposure Limit (HBEL) such that there can be broad guidance on the extent of Quality Risk Management (QRM) and control measures required?
A: Firstly, it should be recognised that hazard varies on a continuum scale and that there are no firm cut off points, risk should be controlled on a proportionate basis. However, as a broad hypothetical model the following figure could be considered to show the increasing level of hazard (red being highest hazard) presented by products and there should be a commensurate increase in the level of control to prevent potential cross contamination in a shared facility. Actual HBEL values should be used in QRM studies to determine the actual controls required.

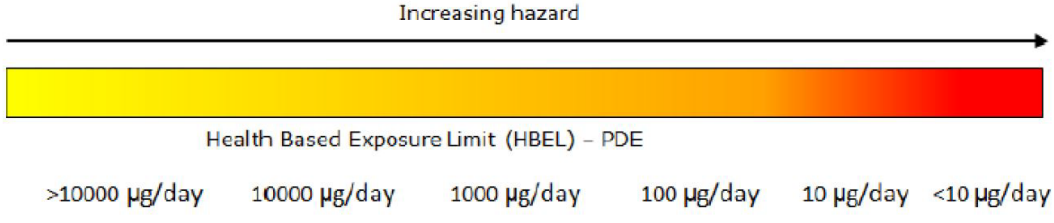

Diagram developed from an original concept published by ISPE. Source: ISPE Baseline® Pharmaceutical Engineering Guide, Volume 7 – Risk-Based Manufacture of Pharmaceutical Products, International Society for Pharmaceutical Engineering (ISPE), Second Edition, July 2017.

Q3. How should manufacturers use the HBELs?
A: The role of HBELs in determining cleaning limits is explained in Q&A 6. However, the purpose of generating HBELs goes beyond justification of cleaning limits. Once the health-based assessment has been completed and the HBEL confirmed, these data should be used via a Quality Risk Management process to determine what controls need to be put in place and to assess if existing organisational and technical control measures are adequate or if they need to be supplemented. This Quality Risk Management process should be carried out prospectively in the case of new equipment/facility to determine what control measures are required. It is expected that for products which present a higher potential harm to patients/animals, more elaborate organisational and technical control measures will be required. Using a structured Quality Risk Management process, manufacturers should consider the risks of cross contamination down to the established level from the HBEL. During the QRM study manufacturers should consider how easily such a quantity of contamination could occur, without detection, at batch and unit dose level. The level of detail in the QRM process should be commensurate with the potential harm as indicated by the HBEL and the suitability of control measures supported by practical and science-based evidence. Manufacturers should be mindful that cross contamination controls implemented previously may not adequately assure control of the cross-contamination risk in the context of the HBEL approach. Additional observation of working practices, investigation and analysis may be required to provide full practical confidence in the effectiveness of controls. Where control measures cannot adequately assure that the potential contamination is consistently controlled to a level below that of the HBEL then the products concerned should be manufactured in dedicated facilities.

Q4. What competencies are required for the person developing the Health-Based Exposure Limits (HBEL)?
A: Health-Based Exposure Limits should be determined by a person who has adequate expertise and experience in toxicology/pharmacology, familiarity with pharmaceuticals as well as experience in the determination of health-based exposure limits such as Occupational Exposure Levels (OEL) or Permitted Daily Exposure (PDE). Where experts are contracted to provide the HBEL, contractual agreements in compliance with Chapter 7 requirements should be in place prior to work being conducted. It is not considered acceptable for manufacturers to 'purchase' HBEL assessments without recording an assessment of the suitability of the provider (including the specific technical expert) as a qualified contractor.

Q5. What responsibility do contract givers have to contract manufacturers in relation to data to support a HBEL assessment?
A: Contract givers should either provide a full HBEL assessment to contract manufacturers or provide the data to allow the contract manufacturer to conduct the HBEL assessment. In either case the HBEL assessment, including data references and relevant experts should be available on request during inspection of the manufacturer. Page 2/4

Q6. How can limits for cleaning purposes be established?
A: Although the EMA guideline (EMA/CHMP/CVMP/SWP/169430/2012) may be used to justify cleaning limits (as per Introduction paragraph 3), it is not intended to be used to set cleaning limits at the level of the calculated HBEL. For existing products, manufacturer's historically used cleaning limits should be retained and can be considered alert limits provided that when taking cleaning process capability into account, they provide sufficient assurance that excursions above the HBEL will be prevented. A similar process should be adopted when establishing cleaning alert levels for products introduced into a facility for the first-time.

Results above the alert cleaning limit should trigger an investigation and, where appropriate, corrective action to bring the cleaning process performance within the alert cleaning limits. Repeated excursions above the alert cleaning limit will not be considered acceptable where these indicate that the cleaning method is not in control. Recognised appropriate statistical methods may be used to determine whether the cleaning process is in control or not.

Q7. Is analytical testing required at product changeover, on equipment in shared facilities, following completion of cleaning validation?
A: Analytical testing is expected at each changeover unless justified otherwise via a robust, documented Quality Risk Management (QRM) process. The QRM process should consider, at a minimum, each of the following:

- the repeatability of the cleaning process (manual cleaning is generally less repeatable than automated cleaning);
- the hazard posed by the product;
- whether visual inspection can be relied upon to determine the cleanliness of the equipment at the residue limit justified by the HBEL.

Q8. What are the requirements for conducting visual inspection as per Q&A 7?
A. When applying visual inspection to determine cleanliness of equipment, manufacturers should establish the threshold at which the product is readily visible as a residue. This should also take into account the ability to visually inspect the equipment, for example, under the lighting conditions and distances observed in the field. Visual inspection should include all product contact surfaces where contamination may be held, including those that require dismantling of equipment to gain access for inspection and/or by use of tools (for example mirror, light source, boroscope) to access areas not otherwise visible. Non-product contact surfaces that may retain product that could be dislodged or transferred into future batches should be included in the visual inspection. Written instructions specifying all areas requiring visual inspection should be in place and records should clearly confirm that all inspections are completed. Operators performing visual inspection require specific training in the process including periodic eye sight testing. Their competency should be proven through a practical assessment.

Q9. Is it acceptable to simply segregate products of a common therapeutic classification in a dedicated area as a means of controlling risk of cross contamination?
A: Manufacturers cannot just segregate common products from other product types as a means of dealing with the risk to patient and animal safety. Although this may prevent contamination of other product classes it does not address the possibility for cross contamination within product classes. The approach taken to control cross contamination between individual products within a class produced in the same dedicated area should follow the principles in Q&A 3. This should include implementation of appropriate organisational and technical control measures to prevent contamination between such products within product specific HBELs.

Q10. Is the use of LD50 to determine Health-Based Exposure Limits for drug products acceptable?
A: No, LD50 is not an adequate point of departure to determine a HBEL for drug products.

Q11. Can Ectoparasiticides be manufactured or primary packed in common equipment with other categories of medicinal products for human or veterinary use?
A: If a HBEL cannot be determined or data cannot support manufacture in shared facilities then the Ectoparasiticides should be manufactured in dedicated facilities.

Q12. What needs to be taken into account when manufacturing Veterinary Medicinal Products for different species in the same facility?
A: The guideline on setting health-based exposure limits indicates that the carry over limit should generally be derived using the human HBEL. However, in cases where there is concern relating to known susceptibility of a particular species (e.g. monensin in horses) the HBEL approach should take into account knowledge of specific animal toxicity when evaluating products manufactured in shared facilities/equipment.

Q13. Should the HBEL be re-assessed throughout the phases of development of Investigational Medicinal Products (IMPs)?
A: Health-Based Exposure Limits should be established based on all available data, and particularly as the knowledge base for IMPs is continually evolving the basis for establishing the HBEL, should be regularly reviewed taking account of any new relevant data.

- Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities

1.1.4 EU GMP guide part I: Basic requirements for medicinal products: Chapter 5: Production

1. Is it possible to use multiple batch numbers in packaging of medicinal products? H+V December 2020

GMP inspectors have discussed the desirability of more than one batch number appearing on the packaging of medicinal products.

It is normal practice for companies to use a bulk batch number that is different from the finished product batch when the bulk is packaged as several sub-batches. There is normally an element in the numbering format common to the bulk batch and finished product batches that clearly ties these together. The difference normally takes the form of a suffix, prefix or both.

A matter of concern for the inspectors is when the bulk and finished product batch numbers are completely different and there is no obvious connection between the two. Even though the manufacturer has a system of traceability, the inspectors agree that this is an undesirable practice and should be avoided. The main reasons for this are:

- patients and healthcare professionals may mistakenly believe that there has been a packaging error;
- hospitals often remove products from the outer packaging and traceability may therefore be lost;
- confusion may occur in the case of recall, rendering such action potentially ineffective.

It is accepted that there may be exceptional cases where multiple batch numbers are displayed on a pack, such as in combination product packages. Manufacturers are recommended to discuss individual cases with the relevant supervisory authority. In all cases, traceability must be maintained.

2. What are the expectations with regard to documentation and verification of the supply chain for active substances (ref. Paragraph 5.29, Chapter 5 EU GMP Guide)? H+V August 2015

The supply chain for each active substance must be established back to the manufacture of the active substance starting materials. This should be documented and must be kept current. The risks associated with this supply chain should be formally documented. Control of each incoming consignment of active substance should include verification that it has been received from the approved supplier and approved manufacturer. The entire supply chain should be verified for a supplied batch periodically to establish a documented trail for the batch back to the manufacturer(s) of the active substance starting materials. The frequency of this verification should be based on risk.

3. Is it acceptable to pack (primary and/or secondary packaging) multiple batches of the same product (e.g. tablets, capsules, lozenges) in order to obtain a single batch as a super batch? H+V July 2018

Normally, such an approach should be avoided as each batch is made from the same initial quantity of material and should remain as an individual batch of finished medicinal product bearing a unique batch number. Therefore, any other approach should be thoroughly justified by applying the principles of Quality Risk Management (QRM) taking into account at least the following criteria:

- length of time the equipment has been in use;
- pharmaceutical form of the drug product that cannot be homogenised (tablet, capsules, etc);
- expiry date of the drug products;
- ongoing stability study design and results;
- reference samples plan for each batch;
- criticality of the drug product and the risk of shortage that may arise from any quality issue;
- prior approval of the MAH.

Irrespective of the outcome of the QRM, such an approach can only be accepted if each individual batch of the combined "super batch" undergoes all the in-process control and finished drug product testing as specified in the marketing authorisation dossier.

In the event of a recall, the entire super batch should be recalled.

4. What are the requirements for batch numbers appearing on the packaging of medicinal products subject to parallel trade? December 2020

Medicinal products that are relabelled or repacked with the purpose of parallel trade should be in compliance with any specific national legislation or guidance in relation to the batch number(s) that are to be present on the parallel distributed traded packs.

In the absence of specific national legislation or guidance, the outer packaging should have only one batch number, as allocated by the parallel trader. This batch number allocated by the parallel trader should incorporate two components; (1) the batch number of the original pack and (2) a unique code identifying the repackaging/relabelling run. The code for the repackaging run may comprise numbers or letters or a combination of both. The parallel trader's batch number should be such that Component 1 above (originator

batch number) is followed by Component 2 (a code related to the repackaging/relabelling run on that batch). Any deviation from this approach should be presented to and should be authorised by the supervisory authority. The traceability between the original batch number and the parallel trader's batch number should be documented in the manufacturer's repackaging records.

In the case of human medicinal products, the unique identifier generated by the parallel trader when (re)placing safety features should reflect the 2 component batch number as described above. The link between the original batch numbers and parallel trader's two component batch number should be maintained in the EU repositories system as per Article 34(4) of Commission Delegated Regulation (EU) 2016/161. Any batch number applied to the primary packaging components (e.g. blister strips, bottle labels, etc.) during the repackaging operation should be the same as that applied to the outer carton of the repackaged/relabelled product.

5. What are technical and organisational measures that should be taken into consideration to prevent microbial contamination of non-sterile medicinal products

Background

The likelihood of non-sterile medicinal products being contaminated by microbes is closely linked to the manufacturer's processes, particularly in terms of how well cleaning and gowning protocols are followed. To minimise the risk of product quality defects the following Q&A´s highlights technical and organisational measures that should be taken into consideration to prevent microbial contamination of non-sterile medicinal products.

The importance of proper controls of microbiological contamination in non-sterile products is also supported by individual cases of multi-resistant microorganism present in non-sterile antibiotics

Chapter 5, section 5.10 of the GMP guidance stresses the significance of protecting products and materials from microbial and other types of contamination at every processing step, albeit without delving into specifics. Further guidance can be found in the scope of Annex 1 and Annex 15.

Even for a non-sterile product, a microbial contamination might pose a hazard for the product or the patient, such as opportunistic microbes in the final formulation or multi antibiotic resistant microbes. Consideration should be taken for such risks, applying QRM principles similar to chapter 5.17 - 5.22 EU GMP guide part 1.

Special focus is expected for cleaning of equipment in accordance with cleaning validation principles. In general, critical cleaning procedures should be thoroughly explained in SOPs, verified and properly documented during execution.

Q1 What other measures should be taken into consideration to prevent microbial contamination of non-sterile medicinal products?

A1
Facility/equipment design and use, material flow, microbiological controls process characteristics, and cleaning processes may be considered in relation to established limits. The results of the Quality Risk Management process should drive decisions on implementing various technical measures. Manufacturing plants may consider using principles from Contamination Control Strategy (CCS) in accordance with Annex 1 guidance. Based on the outcome of the Risk Management process the following technical measures may be included:

- Inclusion of suppliers of detergents/ cleaning agents in the supplier evaluation program.
- In the event of a deviation, it is important to consider implementing a phenotypical identification strategy for growths for further assessment.
- The expiry date of solutions of cleaning agents and detergents should be considered. When preparing these solutions, care should be taken to ensure that the preparation does not constitute a source of contamination.

Measures described in EU GMP Part 1 should be included if relevant:

Cleaning validation study should include microbiological samples of surfaces that get into direct contact with the drug product in order to determine the cleaning success with appropriate documentation of sampling

locations and techniques explained. The cleaning validation study should also incorporate other parameters of the cleaning process, such as the drying step, in order to prevent microbial contamination from residual humidity in the equipment.

Validated methods should be used for microbial contamination testing of the APIs, excipients, water, primary packaging materials, equipment, the environment and finished products.

Water used in the manufacture should be demonstrated to be suitable for its intended use.

In case of microbial contamination, it is expected to use validated cleaning methods and/or disinfection methods. When area disinfection is performed either scheduled or when needed, (e.g. microbial contamination) it should be demonstrated that the detergents/cleaning agents are suitable for their intended use.

Q2 What organizational measures should be taken into consideration to prevent microbial contamination of non-sterile medicinal products?

A2 Based on the outcome of the Risk Management process the following organisational measures may be included among others:

- Proper gowning should be in place including gloves and facemasks at critical operations.
- Glove disinfection should be considered before entering critical areas.

Organizational measures described in EU GMP Part 1 should be included if relevant:

- Personnel performing gowning and cleaning should receive regular practical training and assessment in disciplines.
- Training of production personnel should include correct behaviour during production activities and other critical activities
- Personnel hygiene and health status should be closely monitored and reviewed.
- Environmental monitoring should be in place to ensure that the facility is suitable for manufacture and there is no risk of contamination

References
EU GMP Chapter 5, 5.21, Technical Measures: vii (e.g. polishing brushes), viii, ix, x, xi, xii, xiii
EU GMP Chapter 5, 5.21, Organisational Measures: iii, v, vi, vii, viii, ix, x
EU GMP Annex 1 (with proper modifications): 4.5, 4.7, 4.8, 4.34, 4.35, 6.18, 7.7, 7.8, 7.9, 7.13 (iii&iv), 9.4 (i&ii), 9.5, 9.6, 9.8, 9.11, 9.12, 9.13, 9.30 (Grade D), 9.31 (Grade D), 10.2, 10.9, 10.10
EU GMP Annex 15: 10 EU Guideline 2015/C 95/02 EU Guideline CHMP/CVMP/QWP/496873/2018 Guideline on the quality of water for pharmaceutical use
ICH Q9 Quality Risk Management

1.1.5 EU GMP guide part I: Basic requirements for medicinal products: Chapter 7: Outsourced activities

1. Are direct agreement a requirement between the MAH, MIA holder responsible for QP certification and sites involved in the various stages of manufacture, importation, testing and storage of a batch before it undergoes certification? July 2023

Chapter 7 describes that a written Contract between the Contract Giver and the Contract Acceptor must be established and where the marketing authorization holder (MAH) and the manufacturer are not the same, appropriate arrangements should be in place, taking into account the principles described in chapter 7. Are direct agreement a requirement between the MAH, MIA holder responsible for QP certification and sites involved in the various stages of manufacture, importation, testing and storage of a batch before it undergoes certification?

A direct written contract should be in place between MAH and the MIA holder responsible for QP certification of the product.

A direct written contract should also be in place between the MIA holder responsible for QP certification of the product and sites involved in the various stages of manufacture, importation, testing and storage of a batch before it undergoes certification (hereafter: contract manufacturers). It is also acceptable to have a direct written contract between multiple parties, such as MAH and MIA holder responsible for QP certification of the product and contract manufacturers or any other entities included in the manufacturing/supply chain, provided that relevant activities and responsibilities for each entity are clearly defined.

A "chain of contract" setup may exceptionally be acceptable instead of direct written contracts as detailed above, provided the following principles are adhered to:

1. It should be ensured that robust and timely communication between the MAH, the MIA holder responsible for QP certification and the contract manufacturers is secured through the "chain of contracts".
2. The MIA holder responsible for QP certification should have access to all of the contracts in the "chain of contracts". Contract manufacturers should have access to those contracts in the "chain of contracts" relevant to the activities they perform and the associated responsibilities. As per EU GMP Chapter 4 all of these contracts are to be considered as part of the Pharmaceutical Quality System.
3. The MIA holder responsible for QP certification should accept in writing the arrangements taken in the "chain of contracts" after performing a written assessment of their suitability and functionality. The assessment should be carried out with a view to ensure, that the "chain of contracts" sufficiently addresses the requirements mentioned in EU GMP Chapter 7: 7.14-7.17. The specific setup and products in question and their traceability through the "chain of the contracts" should be taken into account in the evaluation and be covered by the contracts.
4. The MIA holder responsible for QP certification should ensure that if any of the contracts in the "chain of contracts" are changed, such changes are notified to and accepted by the MIA holder responsible for QP release prior to the change of the respective contracts. Such acceptance can be documented by use of e.g. a change control system.
5. The MIA holder responsible for QP certification should ensure that all parties in a "chain of contracts" setup are audited and evaluated as per the requirements mentioned in EU GMP Chapter 7 and Annex 16.
6. All parties in a "chain of contracts" setup should be reflected in the supply chain diagram mentioned in EU GMP Annex 16: 1.7.2.
7. All contracts in a "chain of contracts" setup are to be reviewed as part of the product quality review (PQR) process.
8. The MIA holder performing QP release should have an adequate number of personnel with the necessary qualifications and practical experience (according to EU-GMP Chapter2: 2.1) for reviewing and assessing the records and the results related to the outsourced activities (according to EU GMP Chapter 7: 7.8 This responsibility remains with the MIA holder irrespective of the number of parties involved (cf. EU-GMP chapter 7: 7.11).
9. It should be ensured through the "chain of contracts" the integrity of the records related to the manufacturing activities throughout the retention period is secured at a site holding a MIA. Archiving of documents might be off-site under the responsibility of the MIA-holder.

Regardless of the contract setup used, it must be ensured that all relevant activities and responsibilities for each entity are clearly defined and that the contract setup complies with any additional requirements of the national legislation.

The following terminology are used throughout this document:

Written contract: A contract accordance to the requirements of EU GMP chapter 7. The word Technical agreement as used in EU GMP annex 16 are in this context considered identical to a written contract

Direct written contract: Contract signed between the parties, that actually perform the activities stated in the contract, e.g. the MIA holder responsible for QP certification as a contract giver and the contract manufacturer as a contract acceptor or the MAH as a contract giver and the MIA holder responsible for QP certification as a contract acceptor.

"Chain of contract" setup: A setup where one or more parties (sites/companies) are acting as signatory in a chain of contracts that links them together. Thus, the setup introduces one or several separate legal entities

between the contract giver - e.g. a MIA holder responsible for QP certification and the contract manufacturer as a contract acceptor. In fact, the GMP activities concerned are sub-contracted over one or several levels.

1.1.6 EU GMP guide part I: Basic requirements for medicinal products: Chapter 8: Complaints, Quality Defects and Product Recalls

1. What are the quality defect reporting requirements of EU GMP?

Suspected product quality defects (e.g. product deterioration, packaging mix-up, among others) should be reported to the competent authority with responsibility for the manufacturing site (or importer where the manufacturer is located outside the EEA), and to the competent authority in each EEA market supplied. In case of impact to EU centrally authorised products, the EMA must also be notified. This notification should be prior to taking any market action, unless, as per paragraph 8.26 of Chapter 8, the need for market action is so serious as to warrant immediate action to protect patient or animal health.

Confirmation of a quality defect does not require completion of the investigation. Reporting should be initiated when available information supports the detection of the issue and when the initial assessment of the potential risks presented to patients/animals indicates that it could result in market action. Notification to competent authorities should typically take place within one working day of confirmation that reporting is required.

In cases where a suspected quality defect involves multiple manufacturing sites, reporting responsibilities should be defined in a technical agreement. It is normal expectation that the MAH and site of final EU batch certification should take the lead on reporting, unless otherwise justified.

Manufacturers are encouraged to notify their national competent authority (or EU Supervisory Authority for sites located outside the EEA) of confirmed serious GMP issues with the potential to lead to a suspected product defect requiring market action (e.g. media fill failure, serious equipment failure, etc.). Confirmation of a serious GMP issue does not require completion of the investigation; reporting should be initiated when available information confirms the detection of the issue.

Serious GMP issues which may result in an abnormal restriction in supply should be notified to the MAH and relevant competent authorities in accordance with legal obligations given in Art 23(2) of Directive 2001/83/EC, Art 27 of Directive 2001/82/EC, Regulation 726/2004 and EMA guidance[1]:

> In the event that a medicinal product which is the subject of a marketing authorisation issued by an EEA authority, and which is marketed in another third country (or countries) then *the marketing authorisation holder shall forthwith inform the relevant EU competent authority of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product concerned* (e.g recalls or serious GMP issues). This is even if the particular batch subject to the prohibition or restriction is not marketed in the EEA.

In cases where national competent authorities set additional national expectations regarding what quality defects should be reported and the timelines for reporting, these should be complied with.

[1]http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000238.jsp&mid=WC0b01ac0580024593

2. For the purposes of product recall, at what stage in the supply chain is a product considered to be placed on the market (ref: Chapter 8 paragraph 8.21)?

A batch recall is defined in the Compilation of Community Procedures as "The action of withdrawing a batch from the distribution chain and users. A batch recall may be partial, in that the batch is only withdrawn from selected distributors or users". This definition covers the entire distribution chain from all points following manufacture through to the end user, the patient. Also, it is possible that the MAH or its subsidiaries are actors in the supply chain, acting as the distributor in certain cases. In such cases, the MAH or its subsidiaries should be regarded as also being part of the distribution chain.

A batch of medicinal product is "considered to have been 'placed on the market'" when one of the following takes place:

- A batch has been Qualified Person (QP) certified and has been made available for sale on the stock management system of the pre-wholesaler/primary wholesaler, etc.
- A batch has been QP certified and supplied to a facility where the manufacturer has no further control over when the product is transferred to saleable stock. This applies even if within the pre-wholesaler/primary wholesaler network.
- In the case of supply chain models where the manufacturer or primary wholesaler supplies direct to the customer (e.g. pharmacy), the batch has been placed on the market from the time of the first customer supply of product from the batch.

National competent authorities should be notified of all recall action proposed after the product has been placed on the market. In situations where the MAH can demonstrate that the batch is reconciled without issuing a recall notice, the national competent authority may agree that public recall communication throughout the distribution network is not necessary.

It is acknowledged that certain short expiry products (e.g. radiopharmaceuticals, advanced therapy medicinal products, etc.) may be shipped under quarantine prior to certification. Retrieval of batches during this quarantine period may be managed within the pharmaceutical quality system.

1.1.7 EU GMP guide part II: Basic requirements for active substances used as starting materials: GMP compliance for active substances

1. How can GMP compliance for active-substance manufacturers be demonstrated? H+V April 2011

Directive 2001/83/EC as amended (Directive 2001/82/EC for veterinary medicinal products) states that manufacturing-authorisation holders are obliged to use, as starting materials, only active substances that have been manufactured in accordance with the detailed guidelines on GMP for starting materials. Thus the legislation puts the responsibility on the manufacturing-authorisation holders using the active substance and does not foresee mandatory routine inspections of active-substance manufacturers.

To provide guidance on how GMP compliance of active-substance manufacturers should be established, guidance documents have been published on this website, including the 'guidance on the occasions when it is appropriate for competent authorities to conduct inspections at the premises of manufacturers of active substances used as starting materials' as part of the Community procedures. This document states that it is expected that manufacturing-authorisation holders will normally gain assurance that the active substances it uses are manufactured in accordance with GMP through audit of the active-substance suppliers.

In addition, a number of questions and answers on audits of active-substance manufacturers on this page provide further guidance.

2. Do I need to perform an audit of an active substance supplier if it has been inspected by an inspectorate from a European Economic Area (EEA) Member State and a valid GMP certificate is available? H+V July 2006

Manufacturing-authorisation holders sometimes confuse the role of inspectorates with their own obligations but nevertheless, when inspection reports or GMP certificates issued by European Economic Area (EEA) mutual-recognition-agreement (MRA) partners or other recognised authorities are available, these can provide useful information to manufacturing-authorisation holders.

However, these alone cannot fulfil the statutory obligations of the manufacturing-authorisation holder or the requirements of section 5.29 of the GMP guideline, but the results of inspections may be used together with other supporting information in a risk-based approach by the manufacturer in establishing priorities for its own audit programme of active-substance suppliers.

3. Is an audit performed by a third party acceptable? H+V Apr 2025

The document 'guidance on the occasions when it is appropriate for competent authorities to conduct inspections at the premises of manufacturers of active substances used as starting materials', published as part of the Union procedures, states that it is expected that manufacturing-authorisation holders will gain assurance that the active substances they use are manufactured in accordance with GMP through audit of the active-substance suppliers. Article 46 (f) of Directive 2001/83/EC states: "The holder of the manufacturing authorisation shall verify such compliance either by himself or, without prejudice to his responsibility as provided for in this Directive, through an entity acting on his behalf under a contract". Manufacturers may not have the necessary expertise or resources to conduct their own audits and therefore may contract with third parties to undertake relevant audits. MIA holders may rely on audits carried out by active substance manufacturers on their suppliers of active substance intermediates provided that there is an appropriate contractual arrangement in place between the MIA holder and the manufacturer of the active substance.

Section 5.27 of the GMP guideline requires that the selection, qualification, approval and maintenance of suppliers of starting materials, together with their purchase and acceptance, are performed by staff that have a current knowledge of the suppliers, the supply chain and the associated risks involved.

An audit conducted by the manufacturing-authorisation holder itself should be integral to the manufacturer's quality-assurance system and subject to the basic GMP requirements, *i.e.* conducted by properly qualified and trained staff, in accordance with approved procedures. It should be properly documented. These aspects can be inspected as necessary by the competent authorities.

If a third party is involved, the arrangements should be subject to chapter 7 of the GMP guideline. There should be evidence that the contract-giver has evaluated the contract-acceptor with respect to the aspects described above.

All parties involved should be aware that audit reports and other documentation relating to the audit will be made available for inspection by the competent authorities if requested. This should normally provide sufficient assurance that the results of an audit carried out by the third party are credible, thus waiving the need for an audit conducted by the manufacturing-authorisation holder itself. A third-party contractual arrangement may lead to a conflict of interest arising on the part of one or more of the parties involved. Conflicts of Interest should be regarded as any influencing factor that may affect the judgement of the auditor resulting in an audit report that may not provide a full and impartial assessment against EU GMP requirements.

Therefore, the MIA holder should ensure that there are arrangements in place to assure that any conflicts of interests are declared, and where declared, that they are assessed for their impact on the impartiality of the audit.

Potential conflicts of interest may arise from diverse sources and may include for example:

- An auditor who declares that they have financial, family or social links to the company being audited.
- An auditor who declares that they have previously worked for the company being audited and who may be presented with documents during the audit that were issued, reviewed or approved by them.
- Contract auditors or companies who declare that they stand to make commercial gain from sale or supply of an audit report (particularly to sharing of audit reports between different manufacturing-authorisation holders using the same active substance supplier).
- Auditors who declare that they stand to gain financially from a successful audit outcome, *e.g.* by payment of bonus or payment only on successful outcome or persons contracted as consultants (to advise) rather than specifically to conduct an impartial audit.

Definition of API starting materials, and hence which steps to perform under GMP, is a critical aspect where conflicts of interest may arise, especially in cases where an API intermediate is manufactured at a site different from the final API manufacturing site.

In addition to the arrangements to assure that conflicts of interest are declared, each auditing body should have a quality system that supports the quality and integrity of audits.

Where a conflict of interest has been declared by a third-party auditor or contracting company, they should document the nature of the conflict of interest, the impact it may have on the conduction of the audit and how the overall assessment of the GMP compliance status of the auditee is assured.

This topic should be addressed in the technical contractual arrangements. Any measures taken by the contract-giver should be documented, *e.g.* signed undertakings by the auditors. The absence or presence of conflicts of interest on the part of auditors or contracting parties should be identified.

QPs should ensure that the written final assessment and approval of third-party audit reports includes an evaluation of a declaration or absence of any conflicts of interest made by auditors and/or the contracting parties.

Conflicts of interest may come to light after the QP has relied upon a third-party audit report and it may be necessary for the QP to undertake a retrospective assessment.

The principles outlined above could be used in case of joint audits between different manufacturing authorisation holders or in those cases where the drug manufacturers have jointly contracted the third party auditor and have signed the contract before the audit took place, using the same active substance supplier, provided that the scope of the audits can be shown to be applicable to the active substances of mutual interest.

4. Is it acceptable to perform a remote assessment based on, for example, questionnaires, review of documents, ISO 9000 certification, results of analytical testing and historical experience with the supplier? H+V July 2016

The EEA inspectorates are not generally in favour of 'paper-based audits' *per se* as they do not provide the same level of assurance as on-site assessments, but do accept that they have a part to play in a risk-based strategy.

They may be particularly applicable when recent positive inspection information is available and where satisfactory audits have been concluded in the past. They cannot replace on-site audits of active-substance suppliers but can be a useful interim and temporary measure within the manufacturer's audit programme.

5. How do the new requirements affect importers of medicinal products? H+V July 2006

Importers are manufacturing-authorisation holders and so the obligations under Article 46f/50f of Directive 2001/83(2) apply to them. For importers, the possibility of a second-party audit performed by the third-country manufacturer that uses the active substance as a starting material may be a further option.

Importers are already obliged to ensure that the third-country manufacturer complies with standards of GMP equivalent to those of the European Community and should have established arrangements in line with chapter 7 of the GMP guideline. They should therefore be fully satisfied that the third-country manufacturer has adequately demonstrated that the active substances it uses for products destined for the European Community have been manufactured in accordance with GMP.

Importers may of course choose to verify the standards of GMP at the active-substance suppliers themselves or through a third party. Whichever option is chosen, the questions and answers above are also relevant.

6. Is it possible to ask for a voluntary inspection of an active substance manufacturer? H+V February 2015

First, the responsibility for only using active substances that have been manufactured in accordance with GMPs is placed on the holders of a manufacturing authorisation (MA). An inspection of the active substance manufacturer by an EEA authority does not liberate a MA holder from this responsibility.

Article 111 (1f) of Directive 2001/83/EC and Article 80(1) of Directive 2001/82/EC, have provision for the competent authority of the Member State concerned to carry out inspections of starting material manufacturers at the specific request of the manufacturer. The request for the inspection should be made to

the EEA competent authority where the site is located or, in case of sites located in third countries, to a competent authority where the starting material is used in the manufacture of medicinal products. If this is not the case, any EEA authority can be approached.

There is no guarantee that such a request will be fulfilled since competent authorities primarily use risk-based principles to plan starting material inspections. Thus, when a starting material manufacturer applies for a voluntary inspection, this does not constitute an obligation for the competent authority to trigger an inspection.

7. The notice to applicants requires the submission of a declaration signed by the qualified person (QP) that the active substance used is manufactured in accordance with GMP. … H+V Sept 2008

The notice to applicants requires the submission of a declaration signed by the qualified person (QP) that the active substance used is manufactured in accordance with GMP. The active substance in my product is widely used, but not normally as a pharmaceutical active substance, and I am having some difficulty in confirming compliance. What should I do to furnish the required declaration? H+V September 2008

Full compliance with GMP for finished products and active substances is a legal obligation for manufacturing-authorisation holders. It is recognised that for a small number of medicinal products, the primary use of the active substance is not in a medicinal product and the producer may therefore not be aiming to meet the specific requirements of pharmaceutical customers that represent an insignificant volume of business.

Alternative sources should normally be sought, but in exceptional cases the manufacturing-authorisation holder should assess and document to which extent GMP is complied with and provide a risk-based justification for the acceptance of any derogation.

The declaration provided by the QP should set out in detail the basis for declaring that the standards applied provide the same level of assurance as GMP. The European Medicines Agency will collect experience with this approach, which can be used as a basis for discussion on related amendments to guidelines in the future.

8. During inspections, why do inspectors sometimes ask to see reports of audits of active substance manufacturers carried out by the medicinal product manufacturer? H+V May 2013

Inspectors may need to see audit reports during inspections as part of the assessment of the manufacturing-authorisation holder's systems for confirming GMP compliance of active substance manufacturers or suppliers. Inspectors will expect to see the full details of these reports upon request, including responses received from the audited site, indication of closure of deficiencies raised or commitments made.

9. What are the expectations for the content of written final assessment of third-party audit reports? H+V Apr 2025

The QP has the ultimate responsibility to ensure that audit reports are properly evaluated when the audit is performed by a third party. The written final assessment document should provide a comprehensible summary of this evaluation and should be readily available and shared with authorities, if requested.

The assessment should include all expected elements of the auditing process and audit report(s) identified before, during and after the audit. In particular, this includes verification of contractual arrangements, scope and appropriate duration of audit, adequate competence of auditors considering the scope of the audit, planned audit frequency, and CAPAs whether adequate and how these are to be followed up. Any conflicts of interest identified should be discussed.

10. What expectations do inspectors have for the content of reports of audits of active substance manufacturers carried out by the medicinal-product manufacturer? H+V May 2013

As a minimum, the following is expected to be included in the report:

- The full postal address of the site. The auditors must be identified by full name and their employer recorded. If the audit is conducted on behalf of other parties this should be clear in the report. Where an audit report is obtained through a third party, the manufacturing-authorisation holder is responsible for ensuring the validity and impartiality of the audit report. The identity of key staff participating in the audit should be recorded along with their roles.The full contact details of the person through which the audit was arranged should be recorded including contact details (e-mail address, telephone number). The dates of the audit should be recorded, with the full-day equivalents clarified if full days were not spent on site. A justification should be recorded for the duration of the audit. If, in exceptional circumstances, the audit had to be restricted to fewer days on site than required by the scope of the audit, the reasons should be explained and the conclusions with respect to the GMP status of the site should be justified background information on the active substance manufacturer should be recorded; this should include the company ownership, the age of the site, the number of staff employed in total and for the specific products being audited. The role of the site in manufacture of the active substances being audited should also be clarified for each of the active substances being audited, e.g. if the site performs the full manufacture or only part of the manufacture.
- The scope of the audit should be clearly stated e.g. what activities (against European Union GMP part II / International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Q7 chapters) were covered. The activities which were not covered by the audit should also be clearly recorded. Auditors should identify the high risk areas for audit specific to the site or products being audited. For example, these could include but not be limited to:
    - process, cleaning or validation;
    - risk of cross-contamination with other active substances or other substances;
    - potential for generation of unknown impurities;
    - risk of mix-up of materials and products through materials handling or packing;
    - change control;
    - deviation recording or management;
    - security sealing of active substance containers and security or temperature control of shipments.
- Subsequent audits conducted as part of the ongoing supplier audit program may have a reduced scope focusing on the highest risk areas. In such cases the highest risk areas should be identified and justified.
- A list should be recorded of all active substances directly included in the audit scope plus other active substances or intermediates (or other products) manufactured at the site.

There should be a clear record of the products, the stages of manufacture and the buildings audited. If access was denied to any relevant areas of the site this should be recorded and explained. The list should clarify which of the active substances in the scope of the audit are manufactured in multi-purpose equipment or buildings as either final product or any of the intermediate stages.

- Dates of any previous audit conducted by or on behalf of the same manufacturing-authorisation holder should be recorded. If any of the audits did not conclude with a positive GMP compliance status, a brief summary of the reasons for this should be recorded.
- Each of the applicable sections of EU GMP part II should form sections of the report with a summary of what was examined, the key findings and compliance with the requirements of each section. The report should clearly state findings against each activity audited with particular focus on the high risk areas. Any GMP deficiency identified during the audit must be clearly recorded with its criticality defined. An explanation should be given, in the report or in a supporting standard operating procedure, of the categorisation system used to classify deficiencies, e.g. critical, major or minor.
- Responses to the audit by the active-substance manufacturer should be reviewed by the auditors. Corrective and preventative actions and timescales for completion should be assessed by the auditors to establish whether these are appropriate to the findings. Further clarification or evidence of completion should be requested, commensurate to the risk.
- A summary assessment of the status of corrective and preventive actions should be recorded by the auditors once these have been received and assessed. An overall recommendation should be made in the final report. The summary should include whether the auditor regards the actions as satisfactory. The responsible QP should ensure that he or she, or someone to whom it is delegated, is in agreement with the overall recommendation of the final report. The QP must not release the relevant medicinal products without knowledge of a positive recommendation from the auditors. This

recommendation should include the GMP compliance status of the site and whether any reduced controls on materials receipt at the finished product manufacturing site are supported by the auditors.
- A proposed re-assessment period should be recommended.
- The final report should be signed and dated by, at least, the lead auditor.

11. How should active substance auditors be qualified? H + V May 2013

Auditors should have sufficient scientific, technical and other experience to enable them to perform an adequate and thorough audit of the active substance manufacturer, as related to the planned scope of the audit. Where a proposed auditor lacks an appropriate level of direct experience in the field of active substance manufacture, he or she should undergo a documented training and assessment programme in the areas that are relevant to the audit, taking into account the auditor's anticipated role in the audit and the technologies that are likely to be encountered during the audit. Auditors must also be trained and assessed in their knowledge and understanding of EU GMP part II and in auditing techniques in general. The training and assessment should be fully documented.

The qualification and experience of contracted auditors are the same as the requirements for the manufacturing-authorisation holder's own auditors.

12. What is the frequency for the routine re-inspection of an active substance manufacturer? H+V February 2015

Article 111 (1b) of Directive 2001/83/EC requires that Member States have a system of supervision including inspections at an appropriate frequency based on risk, at the premises of the manufacturers, importers, or distributors of active substances located on its territory.

In line with the document "Model for Risk Based Planning for Inspections of Pharmaceutical Manufacturers" available in the Compilation of Union Procedures, sterile and biological active substances are considered a relatively higher risk. Consequently, competent authorities may decide to submit these substances to a higher or a set inspection frequency.

13. What are the GMP requirements to be applied to the formulation of biological active substances with excipients, when described in the active substance section of a registration dossier? H+V February 2017

The Q&As on Quality Part 1, address the exceptions where the formulation of an active substance can be described under CTD section 3.2.S.

For the manufacture of biological active substances, Part II and Annex 2 of the GMP guidelines apply. While quality risk management principles also apply to the formulation of a biological active substance, some aspects of GMP part 1 as described below are more appropriate and are expected as a minimum:

- Particular emphasis should be put on the management of the constitutive excipients of the formulated active substance. Specifications should be defined for excipients according to GMP Part I., 4.14 and the monographs of the European Pharmacopoeia should be applied. The approval, maintenance and audit of excipient suppliers should be based on quality risk management, in accordance with GMP Part I, 5.29 and the EU guidelines on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use. An agreement between the medicinal product manufacturer and the excipient manufacturer should be established in accordance with GMP Part I, 5.28.

The sampling of excipients used for the formulated active substance should comply with GMP Annex 8 and retention samples of excipients should be kept under the responsibility of the medicinal product manufacturer (in accordance with GMP Part I., 1.9 (viii) and GMP Annex 19).

Excipients used by the manufacturer of the formulated active substance should be included in the Periodic Quality Review (in accordance with GMP Part I., 1.10 (i)).

- Consideration should be given to the inclusion of batches of a finished medicinal product manufactured from formulated active substances, stored for the maximum holding time, in the ongoing stability program of the medicinal product, in accordance with GMP Annex 2, 67 and GMP Part I., 6.28.
- When outsourced, the manufacture of a formulated active substance should be managed in the same way as the outsourcing of the manufacture of an intermediate medicinal product, through full application of the requirements of Chapter 7 of the GMP part I guideline.

14. What are the GMP requirements applicable to the comminution and initial extraction steps in the manufacture of non-transgenic comminuted plants and herbal extracts used as active substances?

Questions and answers on GMP requirements applicable to the early manufacturing steps for comminuted plants and herbal extracts used as active substances
Reference Number: EMA/INS/GMP/48514/2021 English (EN) (118.76 KB - PDF)**First published:** 05/02/2021
View

1.1.8 EU GMP guide part II: Basic requirements for active substances used as starting materials: GMP compliance for active substances in investigational medicinal products (IMPs)

1. Are active substances used as starting materials in the production of IMPs subject to GMP? H July 2006

Directives 2001/82/EC and 2001/83/EC, as amended, include obligations for manufacturing-authorisation holders only to use active substances that have been manufactured in accordance with GMP. Provision is also made for inspections of active-substance manufacturers but only under certain specified circumstances.

IMPs are unaffected because the obligations of manufacturing-authorisation holders in this case are laid down in Directive 2005/28/EC, which does not contain corresponding requirements for active substances. Furthermore, this is made clear in the introduction to part II of the GMP guideline.

Part II of the GMP guideline does include a short section on new active substances to be used as starting materials for IMPs and these remain as recommendations with no mandatory force. Nevertheless, active substances used in the manufacture of marketed products are already required to comply with GMP irrespective as to whether they may also used in the manufacture of IMPs.

1.1.9 EU GMP guide annexes: Supplementary requirements: Annex 1: Manufacture of sterile medicinal products

1. What are the sampling requirements for sterility testing when a finished product batch of a terminally sterilised medicinal product is made up of more than one steriliser load? H+V October 2008

The sampling plan for sterility testing should take account of the definition of a batch as stated in the glossary of the GMP guideline together with the recommendations of the new annex 1 section 10.6, each steriliser load is considered to be an independent sub-batch. Consequently, one sterility test should be performed per sub-batch. The number of samples per steriliser load should conform to European Pharmacopoeia requirements, section 2.6.1.3.

However, Section 8.54 of the new annex 1 and Annex 17 allow the introduction of parametric release to replace sterility testing thus waiving the sampling requirements. A variation to relevant existing marketing authorizations would be necessary.

This introduction implies consideration for the bioburden assay before sterilisation to be performed per batch (annex 1 section 10.4 and annex 17 section 4.9). Consideration should also be given to the "Real Time Release Testing guideline" ref EMA/CHMP/QWP/811210/2009-Rev1 and guideline-sterilisation-medicinal-product and active-substance ref EMA/CHMP/CVMP/QWP/850374/2015

For large-volume parenteral where the sterilisation cycle has been qualified with an overkill level, and in exceptional situation such as insufficient historical data regarding sterility testing to support parametric release, the regulated user can follow an alternative sampling plan in accordance with a specific internal procedure agreed with the supervisory authority (unless already specified in the marketing authorisation). This procedure should state the need to sample from each steriliser load including the coolest location identified during the steriliser qualification. The number of samples per load should be defined based on a risk-based approach and the overall number of samples per batch should conform to European Pharmacopoeia requirements, section 2.6.1.3.

2. What is the maximum acceptable bioburden level? H+V Jan 2024

Update January 2019: This Q&A has been superseded by the Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container. Please refer to this guideline for further information.

The specification limits for bioburden should be NMT 10 CFU/100 ml, in line with the guideline "sterilisation-medicinal-product and active-substance ref EMA/CHMP/CVMP/QWP/850374/2015)".

Note for guidance on manufacture of the finished dosage form - First version and Note for guidance: Manufacture of the finished dosage form).

When a prefilter is installed, unless otherwise justified, a bioburden limit of 10 CFUs/100 ml before first filtration is achievable in principle and is strongly recommended from a GMP point of view. Higher bioburden limits should not be justified by the high capacity of two consecutive bacteria retaining filters.

However, when appropriate justification is submitted (processes involving fermentation or other biological or herbal components, use of purified water for ophthalmic preparations, etc.), a bioburden limit of higher than 10 CFUs/100 ml before prefiltration may be acceptable. In such cases, it should be demonstrated that the first filter has the capability to achieve a bioburden prior to the last filtration of NMT 10 CFUs/100 ml, in line with the notes for guidance on manufacture of the finished dosage form (CPMP/QWP/486/95 and EMEA/CVMP/126/95).

3. Water for injection by reverse osmosis. H+V May 2016

- Questions and answers on production of water for injections by non-distillation methods – reverse osmosis and biofilms and control strategies - Final

4. Is rapid method valid for the detection of microorganism within grade A and B? H+V Jan 2024

Rapid method is one of the alternative monitoring systems that may expedite the detection of microorganisms pending that the requirements of annex 1 points 9.28, 9.30 and 9.31) are fulfilled.

5. Is an isolator considered as a "closed isolator" if the semi-continuous ingress and/or egress of materials during operations is conducted via reproducible bio-decontamination steps (active VPHP material airlock)? H+V Jan 2024

Annex 1 distinguishes two types of isolators:

- Closed isolator systems exclude external contamination of the isolator's interior by accomplishing material transfer via aseptic connection to auxiliary equipment, rather than use of openings to the surrounding environment. Closed systems remain sealed throughout operations;
- Open isolator systems are designed to allow for the continuous or semi-continuous ingress and/or egress of materials during operations through one or more openings. Openings are engineered (e.g. using continuous overpressure) to exclude the entry of external contaminant into the isolator.

An isolator designed to interface with material transfer airlock that uses a reproducible bio-decontamination steps (active vapor-phase hydrogen peroxide (VPHP) decontamination) might be considered as a closed isolator as per Annex 1 glossary definition, provided that the interface can be shown to constitute an efficient

barrier to the surrounding environment based on documented evidence from qualification/validation studies and monitoring data.

For instance. This might be possible , as long as the VPHP cycles are validated and filling chamber environment is protected by the sealed door (as barrier) while the integrity of airlock is broken during loading followed by decontamination cycle before opening the barrier again. Requirements of Annex 1 points 4.10, 4.11 and 4.12 should be considered.

It needs to be pointed out, that these elements should be discussed with the respective supervisory authority.

6. What are the requirements for the bioburden sampling to support parametric release? H+V Jan 2024

Annex 1 point 10.4 states that for products authorised for parametric release, a supporting pre-sterilisation bioburden monitoring programme for the filled product prior to initiating the sterilisation cycle should be developed and the bioburden assay should be performed for each batch (sub batch) The sampling locations of filled units before sterilisation should be based on a worst case scenario and be representative of the batch. Any organisms found during bioburden testing should be identified and their impact on the effectiveness of the sterilising process determined. Where appropriate, the level of endotoxin/pyrogen should be monitored.

Annex 17 point 4.9 states that a pre-sterilization bio-burden monitoring program for the product and components should be developed to support parametric release. The bioburden should be performed for each batch. The sampling locations of filled units before sterilization should be based on a worst-case scenario and be representative of the batch. Any organisms found during bioburden testing should be identified to confirm that they are not spore forming which may be more resistant to the sterilizing process

The company should consider the bioburden by the batch or sub-batch to be sterilized.

A specific consideration should be given to the time between sampling, sterilisation and testing.

Any alternative to this approach should be thoroughly justified and should consider:

- The materials involved including packaging materials;
- Homogeneity of the bioburden within the different sub-batches;
- Presence of the organisms;
- Time between sampling and sterilisation.

1.1.10 EU GMP guide annexes: Supplementary requirements: Annex 6: Manufacture of medicinal gases

1. What is traceability? H+V July 2010

Traceability is the ability to retrieve the history of the manufacturing and distribution operations of a batch of a medicinal product.

The data recorded through the traceability system should allow efficient investigation in case an incident occurs and should allow recalls of (potentially) defective products.

In the case of packaged medicinal gases, the packaging components (shells and valves) are reusable. It is therefore necessary to record additional information, in particular in relation to the use and maintenance of these components.

2. Which items should be recorded in the case of medicinal gases filled into cylinders to enable traceability? H+V July 2010

Packaging components (shells and valves)

The cylinder is the combination of the shell and its valve.

Shell

For safety reasons, shells are individually identified (specific reference). Individual traceability is therefore possible. The date of the last hydrostatic pressure test (or equivalent test) should be recorded.

Valve

Shells may be fitted with simple valves (e.g. pin-index valves) or integrated valves. Integrated valves are individually identified (individual identification reference). Individual traceability is therefore possible. This is not the case for simple valves, which mostly have only a serial number corresponding to a group of valves.

The design of integrated valves, which are medical devices, is complex. These valves are also subject to periodic preventive maintenance operations. In terms of risk, more serious incidents have been reported with cylinders having this type of valve.

Therefore:

- in the case of simple valves, the type of valve should be recorded, as well as the name of the manufacturer and the serial number, if one is available;
- in the case of integrated valves, traceability should be ensured for each valve. Records should include in particular the type of integrated valve (including the version), the individual identification reference of the valve, the name of the manufacturer, the date of the last (or next) preventive maintenance and details of any preventive maintenance performed on the valve.

Shell and valve

Each shell-and-valve combination should be traceable.

Finished product

The manufacturing batch records should include the individual identification references of the cylinders of each batch of finished product (see EU GMP guideline annex 6, section 17, (g) and (m)).

Distribution

The distribution records should include the individual identification references of the cylinders delivered to each customer.

3. What means should be implemented to ensure traceability? H+V July 2010

In practice, depending on the scale of operation, it may be difficult to ensure effective traceability without a computerised system. Use of bar codes or electronic chips on the cylinders may facilitate this. Any computerised system used to ensure traceability should conform to the requirements of annex 11 of the EU GMP guideline.

4. What should be possible through the system of traceability? H+V July 2010

Should a manufacturer of a medicinal gas receive a serious complaint relating to the quality of the medicinal gas itself or the packaging components, the system in place should allow the identification of the affected cylinders and, where necessary, the recall of any affected cylinders from the market.

A defect relating to packaging components may require identification of specific cylinders within a finished product batch or identification of cylinders present in a number of finished product batches in order to establish the extent of any recall required.

For example, an effective traceability system should allow effective recalls of cylinders fitted with defective valves based on:

- specific type, version or manufacturer's batch for the valves;
- maintenance and calibration operations for the valves during a specific time period.

1.1.11 EU GMP guide annexes: Supplementary requirements: Annex 8: Sampling of starting and packaging materials: Glycerol and other excipients at high-risk of DEG/EG contamination

1. What is the background regarding international incidents of contamination of drug components with diethylene glycol (DEG) and ethylene glycol (EG)? H+V April 2024

Diethylene Glycol (DEG) and Ethylene Glycol (EG) have been implicated in at least 30 incidents of excipients contamination, particularly glycerol and propylene glycol, in the last 90 years, resulting in mortality and serious morbidity in patients, especially in the paediatric population, receiving contaminated medicinal products.

The first incident resulting in the death of 107 people in the United States, following ingestion of sulphanilamide elixir containing diethylene glycol was reported back in 1937. Between 1937 and 2021, there have been diethylene glycol-related poisonings in India, China, Panama, Haiti, Bangladesh, Argentina, and Nigeria.

More recently, in 2022 and 2023, the World Health Organization published a series of Medical Product Alerts identifying medicinal products, mostly paediatric formulations, that were contaminated with DEG and EG. Several countries were affected by the contaminated products including Gambia, Indonesia, Uzbekistan, Cambodia, Marshall Islands, Micronesia, Cameroon, and Iraq. The most prominent incident refers to the death of a high number of children in Gambia and Indonesia receiving contaminated syrup formulations.

Such incidents are related to both accidental cross-contamination of glycerol or propylene glycol with industrial grade materials and, in some cases, to intentional substitution. Although the most recent cases of contamination are still under investigation, historical data suggests that:

- pharmaceutical manufacturers of products containing contaminated glycerol or propylene glycol did not perform full identity testing or tests to determine DEG/EG on the contaminated raw material.
- a risk-based approach for testing raw materials at risk of contamination with DEG/EG was either not followed or was completely lacking.
- pharmaceutical manufacturers of contaminated products relied on certificates of analysis (CoAs) provided by the supplier.
- the origin of glycerol or propylene glycol was not apparent from the CoA and the supply chain had not been appropriately qualified.
- purchase of the contaminated raw material was driven by price overlooking GMP guidelines.

2. How is the EU patient protected from similar contamination occurring in EU products? H+V January 2025

EU GMP, and specifically Chapter 5 on supplier qualification and monitoring, requires all manufacturing companies to confirm that all its raw materials are checked on receipt to confirm their identity and quality. Competent authorities expect product manufacturers to routinely ensure that incoming samples of glycerol, propylene glycol, and macrogols (polyethylene glycol) with a relative molecular mass below 1000, are tested according to the relevant European Pharmacopoeia monograph.

The European Pharmacopoeia monographs for glycerol [0496, 0497], propylene glycol [0430], and macrogols [1444] (polyethylene glycol) with a relative molecular mass below 1000 include a specific limit test for ethylene glycol/diethylene glycol.

3. Can I use the derogations of Annex 8 of the GMP to sample only a portion of incoming containers of for glycerol, propylene glycol and macrogols (polyethylene glycol) with a relative molecular mass below 1000? H+V April 2024

It is correct that annex 8 does provide for a relaxation of identity testing of every container, but it also states that this would not normally be possible if brokers or intermediates were involved in the chain of supply. Therefore, according to Annex 8, sampling of only a portion of containers would not normally be possible.

Glycerol, propylene glycol, and macrogols (polyethylene glycol) with a relative molecular mass below 1000, are commercial articles that are widely used in the food and other industries. Generally speaking, the supply chain for glycerol and other excipients tends to be complex and lengthy. The involvement of brokers is common in the supply chain.

4. What steps are expected of manufacturers and importers when purchasing excipients at high-risk of DEG/EG contamination? H+V January 2025

When designing supplier-assurance and incoming-goods-control programmes, companies should consider glycerol, propylene glycol and macrogols (polyethylene glycol) with a relative molecular mass below 1000, as higher-risk materials.

Manufacturers, especially importers, should be able to exhibit a good knowledge of the supply chains and apply this knowledge and principles of quality risk management to their programmes for supply-chain management, in line with Annex 16 point 1.7.2. Inspectors will look to ensure that the manufacturer's basis for qualification of the supply chain is demonstrably robust for higher-risk materials, such as glycerol, propylene glycol and macrogols (polyethylene glycol) with a relative molecular mass below 1000. Unless scientifically justified (as described in Q3 above), identity testing of starting materials and the European Pharmacopoeia limit test for DEG/EG will be performed on each container.

5. The European Pharmacopoeia limit test for DEG/EG involves a gas chromatographic method, which may be difficult to perform on a large number of containers. H+V January 2025

This point is acknowledged and alternative tests are under consideration. The European Pharmacopoeia DEG/EG limit test remains the official method for confirmation of compliance with the monograph.

6. Are there any considerations applicable to the pharmaceutical assessment of marketing-authorisation applications? H+V January 2025

In application dossiers for new marketing authorisations (MAs), or in case of relevant variations for existing MAs (for example, replacement of an excipient) for medicinal products containing excipients at high-risk of DEG/EG contamination (e.g., glycerol, propylene glycol and certain grades of macrogols (polyethylene glycol)), excipient specifications should ensure that the risks from potential DEG/EG contamination are mitigated, i.e., a specification for DEG/EG content is included. Suitable test methods are included in the European Pharmacopoeia monographs for glycerol [0496, 0497], propylene glycol [0430], and macrogols [1444]. The mitigation should be discussed and evaluated in the context of the overall control strategy for the finished product.

Sufficient information regarding satisfactory control of this risk will be required in the dossier before approval of the MA application or variation.

For existing approved medicinal products, no variation application is required, except for those few specific types of variations referred to in the first paragraph. However, as a minimum, the specific European Pharmacopoeia control for DEG/EG should be conducted along with the identity test at receipt of each batch of the high-risk excipients above-mentioned. The excipients are required to comply with the current European Pharmacopoeia monograph, and as the specification approved in the dossier will have been that of the European Pharmacopoeia, the risk of DEG/EG contamination will have been appropriately controlled. Compliance with this requirement can be verified during GMP inspections.

7. My company manufactures products for external use. Does this guidance apply? H+V April 2024

Where a company manufactures products for external use, and when it has justified that the presence of DEG/EG in these products poses a low risk, the omission of the test for DEG/EG on each container may be accepted by the supervisory authority.

1.1.12 EU GMP guide annexes: Supplementary requirements: Annex 8: Sampling of starting and packaging materials: Use of near-infrared (NIR) technology for container-wise identity testing

1. The registered specifications of our starting materials include conventional or pharmacopoeial methods for the confirmation of identity but we wish to use NIR to perform identity testing ..

The registered specifications of our starting materials include conventional or pharmacopoeial methods for the confirmation of identity but we wish to use NIR to perform identity testing on each container of starting materials used in the manufacture of parenteral products. Is the use of this alternative method acceptable?

Annex 8 of the GMP guideline states that the identity of a complete batch of starting materials can normally only be ensured if individual samples are taken from all the containers and an identity test performed on each sample. It is permissible to sample only a proportion of the containers where a validated procedure has been established to ensure that no single container of starting material has been incorrectly labeled. However, the annex goes on to say that it is improbable that a procedure could be satisfactorily validated for starting materials for use in parenteral products.

Unless variations are submitted for all affected products, the registered method for confirming identity should be performed. However, there is no restriction on the performance of additional testing and the use of NIR to confirm container-wise confirmation of identity can provide useful information. Under these circumstances, the requirements of the marketing authorisation will be deemed to have been met by carrying out the registered method for confirmation of identity on a statistically representative composite sample when this is supplemented with NIR analysis of every container.

The NIR method should be validated in line with the recommendations of the guideline on the use of near infrared spectroscopy by the pharmaceutical industry and the data requirements for new submissions and variations.

1.1.13 EU GMP guide annexes: Supplementary requirements: Annex 11: Computerised systems

1. Appropriate controls for electronic documents such as templates should be implemented. Are there any specific requirements for templates of spreadsheets? H+V February 2011

Templates of spreadsheets help to avoid erroneous calculations from data remaining from previous calculations. They should be suitably checked for accuracy and reliability (annex 11 p7.1). They should be stored in a manner which ensures appropriate version control (chapter 4 p4.1).

2. What type of accuracy checks (annex 11 p 6) are expected for the use of spreadsheets? H+V February 2011

Data integrity should be ensured by suitably implemented and risk-assessed controls. The calculations and the files should be secured in such a way that formulations are not accidentally overwritten. Accidental input of an inappropriate data type should be prevented or result in an error message (e.g. text in a numeric field or a decimal format into an integer field). So-called 'boundary checks' are encouraged.

3. Are there any specific considerations for the validation of spreadsheets? H+V February 2011

Validation according to paragraph 4 of annex 11 is required at least for spreadsheets that contain custom code (e.g. Visual Basic for applications). Formulas or other types of algorithm should be verified for correctness.

4. What measures are required to ensure data security of databases? H+V February 201

Data security includes integrity, reliability and availability of data. During validation of a database-based or inclusive system, consideration should be given to:

- implementing procedures and mechanisms to ensure data security and keeping the meaning and logical arrangement of data;
- load-testing, taking into account future growth of the database and tools to monitor the saturation of the database;
- precautions for necessary migration of data (annex 11 p17) at the end of the life-cycle of the system.

5. At which phases of the system life-cycle is risk management recommended? H+V February 2011

Risk management should be applied throughout the whole life-cycle. A first risk assessment should be performed to determine the GMP criticality of the system, i.e. does the system have an impact on patient safety, product quality or data integrity? User-requirement specifications are usually developed with consideration of potential risks and form the basis for the first formal risk assessment.

Complex systems should be evaluated in further more detailed risk assessments to determine critical functions. This will help ensure that validation activities cover all critical functions.

Risk management includes the implementation of appropriate controls and their verification.

6. Are user requirements needed as part of the retrospective validation of legacy systems? H+V February 2011

The way to check whether a computerised system is fit for its intended purpose is to define user requirements and perform a gap analysis to determine the validation effort for retrospective validation. These user requirements should be verified.

7. When do I have to revalidate computerised systems? H+V February 2011

Computerised systems should be reviewed periodically to confirm that they remain in a validated state. Periodic evaluation should include, where applicable, the current range of functionality, deviation records, change records, upgrade history, performance, reliability and security. The time period for revaluation and revalidation should be based on the criticality of the system.

8. What are the requirements for storage time of electronic data and documents? H+V February 2011

The requirements for storage of electronically data and documents do not differ from paper documents. It should be ensured that electronic signatures applied to electronic records are valid for the entire storage period for documents.

9. What are the relevant validation efforts for small devices? H+V February 2011

Small devices are usually off-the-shelf pieces of equipment that is widely used. In these cases, the development life-cycle is mainly controlled by the vendor. The pharmaceutical customer should therefore reasonably assess the vendor's capability of developing software according to common standards of quality.

A vendor assessment needs to be performed and the application needs to be verified against the requirements for the intended use. From the perspective of the regulated industry, the implementation of such a device is driven by an implementation life-cycle. At minimum the following items need to be addressed:

- requirement definition for the intended use including process limitations. This should also include a statement indicating whether data are stored or transferred to another system. As per the definition of a small device, data are not stored permanently but temporarily and are not to be modified by a user. Therefore, limited user access handling is acceptable. It needs to be ensured that parameter data influencing the device's behaviour may not be altered without suitable permission;
- risk assessment, taking into consideration the intended use and the risk to patients for associated with the process supported by the small device;
- vendor assessment;

- list of available documentation from the vendor, especially those describing the methodology used and the calculation algorithm, if applicable. A vendor certificate or equivalent detailing the testing performed by the vendor may also be included;
- calibration certificate, if applicable;
- validation plan according to the risk-assessment results;
- verification testing proving that the device fulfills the requirements for the intended use. It may be equivalent to a PQ-phase.

Small manufacturing devices are sometimes only equipped with microprocessors and firmware and are not capable of high-level administration functions. Moreover, data is often transient in nature in these devices. Due to the latter there is no risk of inadvertently modifying data. An audit trail is therefore not necessary and user access may be limited to those functions of parameter control.

10. What alternative controls are accepted in case a system is not capable to generate printouts indicating if any of the data has been changed since the original entry? H+V February 2011

As long as this functionality is not supported by the supplier, it may be acceptable to describe in a procedure the fact that a print-out of the related audit trail report must be generated and linked manually to the record supporting batch release.

1.1.14 EU GMP guide annexes: Supplementary requirements: Annex 12

1. What quality and GMP standards are relevant/applicable to support the use of an X-ray sterilisation process for Single Use Systems (SUS)?

Sterility is a critical quality attribute and cannot be assured by testing but need to be assured using suitable designed, validated and controlled manufacturing process. Ionising radiation may be used during the manufacturing process for various purposes including the reduction of bioburden and the sterilisation. According to the Ph. Eur. chapter 5.1.1 Methods of preparation of sterile products, for ionisation radiation sterilisation, the reference absorbed dose is 25 kGy, with the possibility to use other doses to achieve a SAL equal to or less than 10-6, if justified and validated.

To assure a reliable sterilisation of Single Use Systems (SUS) components with X-ray radiation used for ionising radiation, two main areas should be investigated:

- Evidence of the sterilisation success by the used X-ray radiation process in view to the individual SUS component
- Evidence that the quality and integrity of the SUS component is maintained by the applied X-ray Energy dose.

Evidence of the sterilisation success
For the sterilisation of health care products (e.g. medical devices) with ionising radiation the international standard ISO 11137, part 1 – 3, "Sterilization of health care products – Radiation" covers the use of X-ray irradiation and describe in detail the requirements for the X-ray sterilisation procedure. Irradiation plants are familiar with the demands and application of the ISO-11137 standards especially from the numerous uses of ionising radiation in the sterilisation of medical devices. Therefore, implementation of ISO-11137 rules on the X-ray sterilisation of SUS should be possible for the irradiation plants to guarantee and prove the success of the sterilisation process.

Evidence that the quality and integrity of the SUS is maintained
X-ray as ionising radiation may start radiation induced chemical processes in the irradiated material which may lead to leachable impurities and declining material integrity (e.g. brittleness), even some time after the irradiation process. The relevance of such radiation induced processes depend on the molecular stability towards ionising radiation of the material irradiated. In view to the often-used plastic materials, also for SUS, degradation of the polymer macro molecules leading to leachables and breaks in the plastic material may be relevant and should be evaluated.

X-ray sterilisation and GMP
The manufacture of sterile products is subject to special requirements in order to minimize risks of microbial contamination, and the Annex 12, in addition to the other relevant part of the EU GMP guidelines, clarifies EU

regulatory expectations regarding the use of ionising radiation in the manufacture of medicinal products. Furthermore, relevant guidance to complement EU GMP and EU guidelines can be found in the ISO 11137 series of standards, considering that, where any requirements in ISO 11137 are in contradiction to requirements stated in EU GMP guideline, or in any other document issued by EMA or Ph. Eur., the requirement of these will apply.

It should be noted, that, even if Annex 12 only refers to two types of irradiation process (Gamma Irradiation from a radioactive source and high energy Electron Irradiation (Beta radiation) from an accelerator), X-rays could also be used for pharmaceutical manufacturing and the principles of Annex 12, as well as the other relevant part of the EU GMP guidelines, should be applied.

Even if the irradiation is performed by contract services, the pharmaceutical manufacturer maintains the overall responsibility for the sterility assurance and the product quality.

A risk assessment should assess and control the risks which may influence the safety, performance, and quality of SUS used in the pharmaceutical industry and support the qualification/validation activities.

Principle:
The validation of the radiation sterilisation process should include several elements that could belong either to the irradiation facility or the pharmaceutical manufacturer, including process validation, IQ, OQ, PQ, and routine monitoring and control. The sterilisation process should be defined and validated and should include, at least, the establishing or transferring of the sterilisation dose, the establishing or transferring of the maximum acceptable dose, and, if needed, the evaluation of the orientation if Page 2/5 EMA/INS/GMP/397209/2023 density affects dose distribution (e.g. containers of liquids). The irradiator and its method of operation should be specified. The following aspects should also be covered and evaluated at least:

- Installation Qualification: For X-ray irradiators, the characteristics of the beam (electron or X-ray energy, average beam current and, if applicable, scan width and scan uniformity) shall be determined and recorded.
- Operational Qualification: Dose mapping shall be carried out to characterize the irradiator with respect to the distribution of dose and variability of dose, and variations in the characteristics of the beam during dose mapping shall be within the limits of the irradiator specification. The relationship between the characteristics of the beam, the conveyor speed and dose shall be established.
- Performance Qualification: An absorbed-dose mapping validation is required to determine the locations and magnitudes of minimum and maximum dose, expected levels of variability during routine processing, the monitoring strategy including the position of dosimetry placement, and any adjustment factors used for process conformity assessments. The dose mapping should also include a process capability assessment to ensure robustness based on the product dose specifications and the loading pattern to be utilized. Dose mapping should be carried out for each processing category and for each conveyor path to be used for processing the defined product. The effect on dose to product of different densities present in the irradiator shall be determined to define product that can be processed together.

Procedures and systems for routine monitoring and control, and to demonstrate the continued effectiveness of the established sterilisation dose, should be implemented. Also, a dose audit is required to be performed at defined frequencies.

2. What studies are expected to be performed to support a switch from an established gamma irradiation sterilisation process to an X-ray irradiation sterilisation process for Single Use Systems (SUS)?

Gamma and X-ray are photon-based ionising radiation processes. In the case of gamma irradiation photons are emitted by a radioactive source like Cobalt-60, while for X-ray irradiation photons are generated by conversion of high energy accelerated electrons (bremsstrahlung photons). The resulting stream of well-penetrating photons interacts in the same way with materials, producing Compton Effect whereby scattered electrons generate the killing effects on microorganism DNA.

As the same fundamental physics apply for both irradiation processes a risk-based qualification approach to implementation of X-ray sterilisation, without repeating all the studies performed with gamma irradiation, is considered justified when switching from gamma to X-ray irradiation sterilisation processes. Prior knowledge gathered from experience gained with gamma sterilisation can be leveraged to determine the extent of testing

required. Existing datasets may be used to evaluate on a case-by-case basis the potential risk of a change to X-ray on product's quality (microbiological and safety attributes) and performance.

Before implementation of an alternative X-ray sterilisation process, and in addition to GMP qualification requirements not detailed in this answer, the following should be **verified as a minimum basis** to demonstrate that it is equivalent or better than the gamma sterilisation method in place:

- Impact of the energy levels on radiation activation: in accordance with ISO 11137-1 and the requirements on the irradiation source as sterilising agent, an assessment of the potential for induced radioactivity in X-ray irradiated material shall be conducted for X-ray energy levels exceeding 5 MeV. The nature and quantity of induced radicals should be shown equivalent for both irradiation modalities. Page 3/5 EMA/INS/GMP/397209/2023

- Minimum dose to achieve SAL of 10-6: when transferring the specified sterilisation dose range from gamma to X-ray, absence of negative impact on the sterility assurance level due to differences in operating conditions of the two radiation sources (e.g. dose rates) should be verified. Verification of the dose is achieved through dose mapping (minimum and maximum dose within the established processes' settings throughout the load configuration) and sterility dose audits ensuring the existing minimum dose remains efficient to achieve SAL of 10-6 as described by ISO 11137-2.

- Impact of the maximum dose on leachables and material attributes: an assessment that the differences in irradiation modalities (e.g. dose rate and temperature) do not detrimentally impact the SUS material through its shelf-life as compared to gamma, should be conducted. A limited component verification testing for extractables using suitable model solvent is considered appropriate as long as low potential impact on product has been determined based on irradiation physics, materials impact assessment and knowledge of the product manufacturing process. Data packages generated by SUS suppliers, contractors responsible for irradiation and/or product manufacturers on specific or representative components, can be referred to. The contact of the SUS component or assembly with the product (or lack thereof), the contact duration, the contact surface area, the role of the SUS and the stage of use in the product manufacture flow, should be taken into account in the risk assessment. Manufacturing process conditions conducive to additional risks (e.g. extreme pHs, high organic solvent content, elevated temperatures), may trigger further studies. The most relevant tests should be selected (e.g. physical, chemical, functional) based on identified key risks. Comparability assessment between gamma and X-ray methods should conclude to equivalent extraction and performance profiles at the same dose range to support that existing qualification data for gamma is applied to X-ray. Any meaningful difference precludes switch from gamma to X-ray without full requalification.

3. When would such a switch in sterilisation process trigger the submission of a variation?

If the sterilisation process and/or site for the sterilisation of Single Use System (SUS) components is not mentioned in the MA dossier, then no variation submission is expected. The internal quality change control procedures and related documents (such as change control assessments, risk assessments, verification or validation data) should be recorded in the manufacturer's Pharmaceutical Quality System (PQS). These procedures and documents may be subject to review on GMP inspection.

If the sterilisation of Single Use System (SUS) components is described in the MA dossier and the current sterilisation process and/or site is defined (e.g. gamma sterilisation), a variation submission will be required to update the dossier to reflect the switch to an X-ray sterilisation process and/or new sterilisation site.

The appropriate category of variation for submitting a change in sterilisation process or sterilisation site for SUS components should be selected as per the EU Variation Classification Guidelines. For example, for human medicines, an unforeseen variation under chapter B.I.a) Manufacture of Active Substance or B.II.b) Manufacture of Finished Product may be appropriate in most instances. Unforeseen ('z') variations are considered Type IB by default; if an applicant intends to propose a different Type of variation, a recommendation on unforeseen variations can be requested according to Article 5 of Commission Regulation (EC) No 1234/2008, with appropriate justification. For veterinary medicinal products a similar approach can be followed; the type of variation should be selected in accordance with the relevant guidelines on variations for veterinary medicinal products.

REFERENCES:

Eudralex – volume 4 - EU Good Manufacturing Practice (GMP) guidelines - Annex 12 USE OF IONISING RADIATION IN THE MANUFACTURE OF MEDICINAL PRODUCTS

ISO 11137 Sterilization of health care products – Radiation – Part 1-3

Ph Eur chapter 5.1.1 Methods of preparation of sterile products

Note for Guidance on The use of Ionising Radiation in the Manufacture of Medicinal Products

EMA Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container

Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures (2013/C 223/01)

EMA Procedural Advice on Recommendations on unforeseen variations according to Article 5 of Commission Regulation (EC) No 1234/2008

Commission Implementing Regulation (EU) 2021/17 of 8 January 2021 establishing a list of variations not requiring assessment in accordance with Regulation (EU) 2019/6 of the European Parliament and of the Council

Guidance on the details of the classification of variations requiring assessment according to Article 62 of Regulation (EU) 2019/6 for veterinary medicinal products and on the documentation to be submitted pursuant to those variations

Procedural advice for requests for the classification of variations not already listed in Commission Implementing Regulation (EU) 2021/17 or EMA/CMDv Guidance on the details of the classification of variations requiring assessment according to Article 62 of Regulation (EU) 2019/6

1.1.15 EU GMP guide annexes: Supplementary requirements: Annex 13

1. At what point of processing or incorporation would an active substance be considered a product intermediate and therefore an IMP? H June 2007

Commission Directive 2001/20/EC defines an IMP as 'a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.'

An active substance would be considered an IMP if presented in a packaged form for use in a clinical trial. Any such packaging operation could only be carried out by a site holding an IMP manufacturing authorisation.

Any form of mixing or processing the active substance with other substances would also result in the need for a manufacturing authorisation for IMPs if the resulting product is to be used in a clinical trial.

Physical processing such as milling of an active pharmaceutical ingredient would not constitute IMP manufacturing.

The above does not refer to reconstitution. Separate guidance on this subject is under development.

2. How can the QP of a site assure compliance with the requirements of the clinical-trial application in situations where a QP may be required to certify a batch before the application is submitted to, or accepted by, the competent authority? H June 2007

The QP of a site that is manufacturing a drug product intermediate should assure that the product is produced and controlled in compliance with the EU GMP guideline, in particular the requirements of annex 13.

A product specification file should be developed with contributions from the QPs and other technical personnel of the sites involved with the other manufacturing activities of the IMP. The sponsor of the clinical trial should also be involved in this process. While this may be in a rudimentary form and contain little detail, it should be developed as knowledge of the product evolves and include specifications for critical parameters and controls. The product specification file should be updated and evolve in line with the product development as envisaged in annex 13.

The development of the product specification file should be managed under a technical agreement or a number of technical agreements between the various manufacturing sites. These should include the QP responsible for the final certification of the product and the sponsor, if the sponsor has already been appointed. In any event, final release of the product to trial sites should take place only when the sponsor has established that the product has been manufactured in compliance with the terms of the approved clinical-trial application (as required by annex 13.44). This is defined in annexes 13.40 and 13.44: 'The sponsor should ensure that the elements taken into account by the QP when certifying are consistent with the information notified pursuant to Article 9(2) of Directive 2001/20/EC.'

3. Is it possible to perform packaging or labelling at the investigator site? H September 2007

This is normally possible only if a manufacturing authorisation has been granted to the site by the national competent authority.

According to Article 9(1) of Directive 2005/28/EC, the "authorisation, as provided for in Article 13(1) of Directive 2001/20/EC, shall be required for both total and partial manufacture of IMPs, and for the various processes of dividing up, packaging or presentation."

However, an exemption to this obligation is foreseen in Article 9(2) of Directive 2005/28/EC: 'Authorisation, as provided for in Article 13(1) of Directive 2001/20/EC, shall not be required for reconstitution prior to use or packaging, where those processes are carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member States to carry out such processes and if the IMPs are intended to be used exclusively in those institutions.' In addition, reference should be made to section 33 of annex 13 in respect of any re-labelling to extend shelf life.

4. Who is responsible for the packaging or labelling activities carried out at the investigator site? H September 2007

The sponsor has the ultimate responsibility for all trial activities performed at the investigator site, but should seek the advice of the QP of the IMP manufacturer, if possible, or the clinical-trials pharmacist at the investigator site regarding:

- adequacy of premises and equipment (storage conditions etc.);
- adequacy of written standard operating procedures;
- training of personnel involved, both on GMP requirements and any protocol specific requirements for the IMPs;
- written instructions to perform activities;
- forms to document the activities carried out;
- checks to be done;
- the keeping of retention samples;
- record-keeping.

5. Who is responsible for the transport and storage conditions when an IMP is transported from the manufacturer to the distributor or investigator sites? H May 2009

The sponsor should exercise control over the entire chain of distribution of IMPs, from manufacture or importation into the EEA, through to supply to the investigator sites, so as to guarantee that IMPs are stored, transported, and handled in a suitable manner.

When an IMP originates from a third country, the importer is responsible for verifying that the transportation and storage conditions for the product are suitable. For products originating within the EEA, the manufacturer is responsible for transportation and storage conditions. The respective responsibilities of the sponsor, manufacturer, importer and, where used, distributor should be defined in a technical agreement.

6. What measures should be taken to ensure that the IMPs are kept under suitable conditions during transportation between the manufacturer or distributor and the investigator sites? H May 2009

Storage conditions during transportation should be validated or monitored using a suitable temperature-measuring device that is capable of showing fluctuations in temperature e.g. Temperature Logger. The choice of method of transport should be influenced by the nature and sensitivity of the product and should ensure timely delivery of IMPs to the investigator sites.

The outer packaging should be labelled showing the final destination, the name of manufacturer or sponsor and the storage conditions required.

7. What measures should be taken to ensure that IMPs are kept under suitable conditions during storage at the investigator sites? H May 2009

IMPs should be packaged to prevent contamination and unacceptable deterioration during storage. The sponsor should determine acceptable storage temperatures and any other required storage conditions for the IMPs (e.g. protection from light).

8. What written procedures should be in place at the investigator site regarding IMPs? H May 2009

The sponsor should ensure that all involved parties (e.g. monitors, investigators, pharmacists, storage managers) are aware of these conditions and the actions to be taken in the event that the conditions are not met.

Where appropriate, there should be a restricted area for the storage of IMPs. The temperature of the areas and equipment used for the storage should be monitored using suitable means, such as a temperature recorder or, as a minimum, a record of the maximum and minimum temperatures, at a suitable frequency (for example, daily).

The sponsor should ensure that written procedures include instructions that the investigator or institution should follow for the handling and storage of IMPs. The procedures should address adequate and safe receipt, handling, storage, where relevant any reconstitution process to be carried out before administration, retrieval of unused product from subjects, and return of unused IMPs to the sponsor (or alternative disposal, if authorised by the sponsor and in compliance with the applicable regulatory requirements).

Procedures should also give instructions on the actions to be taken when defined conditions are not met.

9. What records must be kept at the investigator site regarding the abovementioned procedures? H May 2009

The sponsor should ensure that the documents listed in chapter 8, 'essential documents for the conduct of a clinical trial' of the guideline for good clinical practice are maintained and accessible to those parties authorised to review them.

1.1.16 EU GMP guide annexes: Supplementary requirements: Annex 14

1. Is GMP Annex 14 applicable for APIs derived from human plasma?

Yes. Annex 14 applies to medicinal products derived from human blood or plasma, fractionated in or imported into the EEA. It applies to both the drug substance and the drug product manufacturing. In the case of plasma for fractionation, Directive 2003/63/EC (which introduced the central PMF) lists human plasma as "starting material". Therefore, by definition, plasma for fractionation is not considered to be drug substance/API, but "starting material". Drug substance is the purified API/active substance in bulk form (e.g. Factor VIII purified via fractionation out of the starting material), and drug product is the medicinal product in its final dosage form. EU-GMP Part II includes active substances that are produced using blood or plasma as raw materials.

2. If the extraction of active substances from human blood/plasma occurs at a registered API site, can the responsibilities of the QP per GMP Annex 14 be assumed by person(s) authorized to release intermediate APIs and APIs as specified in GMP II 2.14

Yes. The extraction of active substances from human blood or plasma is the first step in the manufacture of the active substance which will be used in a medicinal product derived from human blood or plasma. There may be differences in how manufacture of this type of active substance is regulated in different Member States with some countries requiring that the manufacturer holds a manufacturing authorization (under Article 40 of Directive 2001/83/EC) whilst others may require registration as an active substance manufacturer (under Article 52a of Directive 2001/83/EC). As such, in the EEA this activity needs to take place at a manufacturing site that is authorized or registered for that activity and in accordance with the relevant GMP guidelines, (Part I or Part II as appropriate, and GMP Annex 14. Likewise for manufacturing sites located outside the EEA, GMP guidelines need to be complied with.

GMP Annex 14 states that the QP of the manufacturing site has the following responsibilities (2.5, 3.3, 4.2, 6.8, 8.2-3):

- general oversight of the steps after collection and testing
- ensuring that audits of blood establishments are performed to confirm compliance with the contract with the blood establishments
- acceptance of suppliers of plasma in third countries
- traceability of the product
- release of plasma for fractionation and confirmation that plasma complies with the applicable requirements
- release of intermediates and final products for further processing or delivery to a different site.

It is recognized that only sites that are authorized for manufacturing medicinal products (MIA holders) are obliged to have a QP and that other manufacturing sites, like sites registered for manufacturing of APIs and sites outside the EEA, do not have that obligation.

Annex 14, paragraph 2.5 allows that subsequent steps after collection (including the freezing of plasma) and testing of plasma take place in a blood establishment under the responsibility of their responsible person. To address this particular situation and to ensure the legal responsibilities of the QP who is certifying the batch of finished product are properly addressed, the fractionation plant/manufacturer should establish a contract, in accordance with Chapter 7 of the GMP Guide, with the blood establishment that defines respective duties and details the requirements in order to ensure compliance. The responsibility stays with the QP of the finished product manufacturer. Likewise, in case of manufacture of APIs derived from human blood or plasma, the API manufacturer's person responsible for release as specified in GMP Part II paragraph 2.14, should be involved in drawing up a technical agreement specifying the respective duties of each party such that the legal responsibilities of the QP performing certification of the batch are fulfilled.

1.1.17 EU GMP guide annexes: Supplementary requirements: Annex 16

1. Can a site have more than one QP performing certification of batches?

EU legislation requires a manufacturer to have at least one QP at its disposal but a site may have more than one QP who may certify batches on behalf of the manufacturer.

2. Can there be more than one QP involved in the certification of a given batch?

Annex 16 of the EU GMP guideline gives guidance in relation to situations where different stages of manufacture of a batch take place at different manufacturing sites.

In such cases, the overall responsibility for correct manufacture of the batch lies with the QP performing final certification of the batch before release for sale. It is also possible that, at a single manufacturing site, different QPs could be responsible for certification of different stages of manufacture of the batch. However, as before, the QP performing final certification before release holds overall responsibility for manufacture of the batch in accordance with GMP and the marketing authorisation.

3. In the context of handling unexpected deviations, what is included in the scope of registered specifications for medicinal products?

In the context of handling unexpected deviations, what is included in the scope of registered specifications for medicinal products? / What is an 'unexpected' deviation? / Does Annex 16 permit QP certification of more than one batch affected by the same unexpected deviation?

In order to satisfy the criteria in Annex 16 section 3 for handling unexpected deviations, all registered specifications for active substances, excipients, packaging materials and medicinal products must be met.

Registered specifications for *medicinal products* include in-process, bulk and finished product specifications which have been included in the MA application.

The criticality of registered in-process specifications may vary depending on the quality attribute tested, the impact to subsequent manufacturing processes and ability to test the quality attribute in the finished product.

It may therefore be possible to accept deviation from an in-process specification where risk assessment confirms that there is no impact to manufacturing process or product quality.

Non-compliance with registered specifications (except where excursions from in-process specifications can be accepted based on quality risk management principles) therefore fall outside the scope of Annex 16 section 3, and the QP would not be able to certify the affected batches under the Annex 16 provisions for handling unexpected deviations.

What is an 'unexpected' deviation?

The process itself should be designed to comply with the registered requirements (fit for purpose). A deviation can be considered as 'unexpected' until the time of discovery. Where the relevant authorities have confirmed the need to avoid supply disruption, repeat deviations thereafter are no longer 'unexpected' but may be considered for QP certification and accepted while corrective and preventive action is in progress and where the provisions of Annex 16 paragraph 3.1 are met.

Planned deviations or deviations that are caused by incorrect communication between marketing authorisation holder (MAH) and manufacturers (e.g. if the MAH fails to notify the manufacturer of relevant changes to the MA) are outside the scope of the paragraph 3.1. The marketing authorisation holder should submit an application for a variation to the marketing authorisation, if needed.

Does Annex 16 permit QP certification of more than one batch affected by the same unexpected deviation?

If more than one batch has already been manufactured and/or tested at the time of discovery of the unexpected deviation, then it is acceptable to consider QP certification of all these batches under the provisions of Annex 16 section 3.

Following discovery, repeated deviations from the manufacturing process and/or analytical control methods should be considered changes, and variations to the affected marketing authorisations must be submitted. In exceptional circumstances to avoid disruption to supply, it may be possible to continue QP certification while corrective and preventive action is in progress; see Q&A on what is 'unexpected' deviation above.

4. How should the traceability of the supply chain of the active substance and medicinal product be documented to support the Qualified Person batch certification and release?

To fulfil the criteria for the process of certification set out in Section 1 of Annex 16, the complete manufacturing and distribution supply chain of the medicinal product and its related active substance up to the stage of certification, should be documented and available for the Qualified Person. Supply chain records should provide adequate traceability and be available in a timely manner, to facilitate amongst others, quality defect investigations and product recalls as provided for in Chapter 8 of Part I of EU GMP, or requests of competent authorities. This means that these records should make it possible to identify, for active substances and medicinal products, all the entities, including suppliers and outsourced activities, involved in the manufacture of a specific batch of the drug product, in line with the registered supply chain.

In addition, and according to Chapter 1 and 5 of Part I of EU GMP, when establishing the supply chain traceability the associated risks should be formally assessed and periodically reviewed with appropriate risk-mitigation measures determined to mitigate any risks identified.

5. Is the "certification" by a Qualified Person (QP) of medicinal product batches not manufactured within nor intended for supply to EU/EEA countries and without physical importation into the EU/EEA, covered by EU legislation? Dec 2025

No, "certification" of batches which have not been manufactured within the EU/EEA nor intended for the EU/EEA market and not physically imported into the EU/EEA, is not covered by EU legislation. EU legislation for the manufacture and importation of human medicines, veterinary medicines, or investigational medicinal products does not provide the QP with a role for the "certification" of such batches, except where the products are intended to be placed on the EU market or used in clinical trials within the EU.

Therefore, this activity is not subject to authorisation, under a manufacturing/import authorisation, or inspection by EU National Competent Authorities.

Accordingly, references to EU legislation shall not be included in documents related to the batch release of medicinal product batches that are not manufactured in the EU/EEA, not intended for supply to EU/EEA countries and not physically imported into the EU/EEA.

1.1.18 Questions and answers on remote batch certification / confirmation by the qualified person (QP) - July 2023

These questions and answers apply to EU/EEA QP certification or QP confirmation, as described in EU GMP, and specifically in Annex 16. It is applicable to the manufacture and importation of human and veterinary medicinal products as well as investigational medicinal products.

1. Is remote batch certification / batch confirmation by the QP (i.e. when not at the authorised site address specified on the MIA) allowed?

Remote batch certification / batch confirmation could be allowed if accepted by the national competent authority where the authorised site is located. Some competent authorities may have specific requirements regarding the implementation of remote batch certification / batch confirmation on a routine basis. Manufacturers and QPs should ensure that they comply with any applicable local requirements. In order to determine what requirements apply, manufacturers should consult with their national competent authority.

2. Where remote QP certification / confirmation is allowed, what conditions should apply?

The following points should be taken into consideration:

- It is a prerequisite that the QP certification/confirmation is carried out in full accordance with EU legislation and EU GMP guidelines
- QP certification / confirmation should take place within the EU/EEA (or Northern Ireland) in all cases. This should be demonstrated by technical means.
- QPs are obliged to maintain their knowledge in relation to the products, manufacturing processes and pharmaceutical quality system. QPs also need to be satisfied that their ongoing reliance on the relevant pharmaceutical quality system is well founded. The QP must be able to demonstrate to the competent authority knowledge of the product and the manufacturing processes for which they are responsible. This should include time spent physically on-site as applicable.
- Where remote QP certification / confirmation is employed on a routine basis, it must be described and controlled within the pharmaceutical quality system and relevant detailed site procedures should be in place. In Member States where use of contract QPs (i.e. a person who is not an employee of the manufacturer but conducting QP activities under the manufacturer's authorisation) is permitted, the technical agreement between the MIA holder and the QP should also mention remote certification / confirmation, and specify the circumstances under which the QP must attend the site.
- The QP should have access to all information (data and computer system applications) which are necessary according to Annex 16 to make a decision on batch certification / confirmation.
- The MIA holder should provide the required facilities to enable QPs to carry out their functions remotely. This includes the equipment and support required to enable electronic batch certification / confirmation and completion of the batch certification register remotely. IT systems used for remote batch release should comply with requirements of EU GMP Annex 11.
- All actions carried out by the QP electronically at the remote location should be contemporaneously available for inspection by the competent authorities at the authorised batch release site. It is the responsibility of the MIA holder to guarantee that a) only the QP has editing access to the batch certification function, b) that data being transferred are complete and unchanged and c) an electronic signature, reflecting requirements in annex 11, is in place. QPs must be able to demonstrate that they are fulfilling their wider duties in accordance with Annex 16.
- Compliance with the above points should be verified e.g. as part of the self-inspection programme at the authorized batch release site.

3. What are the technical terms minimum requirements for the remote access and the signature used for batch certification / confirmation?

The risk with regard to IT-security and data integrity for remote access is higher than for access within the controlled environment at the authorized site. Minimum requirements depend very much on the state of technology employed. The following requirements should be adapted to reflect current technological developments. Technical and organisational solutions which are not listed below but result in an appropriate level of security may also be acceptable:

- Prior to transfer of any hardware off-site it should be identified and inventoried. It should be ensured that the hardware remains complete and up-to-date. The hard disk should be encrypted and any ports that are not required should be disabled.
- For QPs who may be using a virtual private network, security parameters on the network operating system, database and application level should be configured appropriately to avoid unauthorised access.
- Recognised industry standards should be used for authentication and authorisation (e.g. two-factor or multifactor authentication). There should be no use of shared authentication information, and automatic expiry of authentication information should be employed.
- Data in transfer should be secured by strong transport encryption (e.g. TLS 1.2, https)
- The MIA holder is responsible for putting organisational controls (e.g. assignment of individual privileges) and technical controls in place to ensure that only the QP is able to perform remote batch certification / confirmation.

1.1.19 Question and answer on residency of the qualified person(QP) - July 2023

1. Is the QP required to be a resident in the Member State where the authorised site is located?

There are currently no harmonized requirements concerning residency of QPs in the EU legislation. However, some Member States may have specific national requirements.

1.1.20 EU GMP guide annexes: Supplementary requirements: Annex 19: Reference and retention samples

1. Is it necessary to retain a sufficient number of samples of each batch of a sterile medicinal product in order to carry out a sterility test on two separate occasions? H+V October 2008

For retention purposes, it is not necessary to keep the full number of samples required in table 2.6.1.3 of the European Pharmacopoeia sterility test monograph to repeat the sterility test performed for release purposes, but only a sufficient quantity to allow the carrying out, on two occasions, of a confirmatory test using the minimum quantities described in table 2.6.1.2 of the monograph.

2. In which cases does the exemption for a fully packaged unit as retention sample apply as referred to in section 2.1 of EU GMP Part I, annex 19? H+V December 2013

In which cases does the exemption for a fully packaged unit as retention sample apply as referred to in section 2.1 of EU GMP Part I, annex 19: "There may be exceptional circumstances where this requirement can be met without retention of duplicate samples e.g. where small amounts of a batch are packaged for different markets or in the production of very expensive medicinal products"? H+V December 2013

Firstly, the supervisory authority should grant such an exemption upon request from the manufacturer. The relevant authority may agree to this when one or more of the following criteria are met:

- A batch size of less than 50 units;
- High value/low volume medicinal products and the high value price of the medicinal product as determined by each individual competent authority;
- Large size of one packaged unit e.g. some veterinary pre-mixes or hospital packages.

Parallel imported/distributed medicinal products will not be granted an exemption from keeping a fully packaged unit if the products have been re-packaged.This is because the exemption refers to "duplicate samples", and in these cases no reference sample is required to be kept by the parallel distributor/importer.

On the other hand, where the secondary packaging of the source product is not opened by the parallel importer/distributor only samples of the additional packaging material used needs to be retained.

3. In those cases where the supervisory authority agrees that the criteria mentioned in the answer to question 1 are met, what should be retained instead of a fully packaged unit? H+V December 2013

The original batch specific primary packaging material with print/imprint, if any, all the original batch specific secondary packaging materials e.g. labels and leaflets with print/imprint including Braille, and dosing aids, if any, must be kept.

The use of photocopies of the fully packaged unit to replace the retention sample are not acceptable as some details e.g. braille and holograms may not show correctly.

4. Do different requirements for reference and retention samples apply for some medicinal products? H+V December 2013

The requirements pertaining to retention samples for investigational medicinal products are covered in annex 13. There may be specific national requirements for compassionate use medicinal products, extemporary produced pharmacy products etc.

1.1.21 Implementation of 3DP technology (Additive Manufacturing Technology) for solid oral dosage forms

1. Introduction

Three-dimensional printing (3DP) is an emerging technology with great potential in pharmaceutical applications, providing an innovative manufacturing solution for patient centred dosage forms.
3DP is an umbrella term, including a variety of different printing technologies that permit the manufacturing of solid structures by depositing successive layers of materials. Dosage forms are produced from a digital 3D file, such as a computer-aided design (CAD) drawing.
The 3DP technology can benefit finished product design by facilitating patient-centric treatment and by developing personalised medicines with e.g. a wide spectrum of dosage levels, shapes, flavours, colours, or drug combinations, all tailored to the specific needs of each patient or disease condition. These characteristics make this technology particularly advantageous for diverse patient groups, including paediatrics, geriatrics, those on multiple medications, and individuals with rare diseases. Moreover, 3DP can integrate rapid manufacturing, with compact equipment, fewer production steps, automated and digital production processes, and a faster changeover, e.g. for small-scale solid dosage forms production.

2. Scope of the Questions and Answers

The aim of this document is to provide guidance on Quality and Good Manufacturing Practice (GMP) requirements to support the use of 3DP technology in pharmaceutical manufacturing of solid oral dosage forms. This document focuses on some specific Quality and GMP requirements but should be read in conjunction with all other relevant EU guidelines.
This document is applicable to both human and veterinary medicinal products covered by a marketing authorisation according to Directive 2001/83/EC or Regulation (EU) 2019/6.
The principles here described may also be relevant in the context of investigational medicinal products for Clinical Trial Applications (according to Regulation (EU) No. 536/2014, article 9 of the Regulation (EU) 2019/6, and EMA/CHMP/QWP/545525/2017 Rev. 2), and applicants are advised to liaise with the relevant National Competent Authorities (NCAs) responsible for the approval and supervision of their clinical trials.
Pharmacy preparations according to Directive 2001/83/EC, article 3, are regulated according to National legislation requirements, in which applicants are advised to liaise with the relevant NCAs.

This document may evolve in the future, as the use of this technology evolves and more pharmaceutical applications are seen.

3. What quality requirements are relevant and applicable to support the use of 3DP in pharmaceutical manufacturing?

Pharmaceutical Development

The choice of a 3DP technology may depend on the active substance properties (e.g. solubility, melting point, degradation temperature, biopharmaceutical classification system (BCS) class, etc.), the selection of feed material(s), and the intended scale of production.

The properties of the active substance(s) and the excipient(s), and the manufacturing operations that are critical to product quality and safety and relevant to product performance and manufacturability, should be defined during pharmaceutical development.

Depending on the technology and the printer used, properties that may impact product and process performance are for instance:

- Rheological properties and extrudability/printability profile of the formulation to be printed.
- Physical state (crystalline or amorphous) of the active substance within the printed dosage form (and its related impact on dissolution/PK behaviour).
- Particle size of the raw materials.
- Compatibility of the active substance(s) with excipient(s).
- Stability of the active substance(s)/excipient(s) (including, e.g. stability towards printing temperature).

The impact of the 3DP technology and the manufacturing process on the properties of the finished product should be evaluated. The characteristics and/or critical quality attributes (CQAs) of the printed dosage form which should be considered and investigated include, but are not limited to:

- Appearance e.g. appropriate size, colour and shape for the specific patient group(s) or animal species.
- Uniformity of mass/content.
- Disintegration.
- Dissolution (and its influence on bioavailability and, if applicable, on bioequivalence).
- Porosity (and its related impact on mechanical strength, disintegration and dissolution).
- Assay and degradation products.
- Stability of the finished product (including considerations to, e.g. different strengths, batch sizes as relevant).

Some 3DP processes include the use of cartridge, or syringe, containing the formulation to be printed. The cartridge/syringe formulation may include active substance(s), excipient(s), or mixtures of ingredients. These intermediate products are often referred to as pharma inks. Several materials can be used in 3DP manufacturing, e.g. polymers, that can be used for their melting, solidification and binding properties under controlled conditions or solvents. These materials serve as carriers for active substances, which are highly adaptable to create complex and customised drug delivery systems, while ensuring uniform dispersion and, in some cases, controlled release.

Cartridges/syringes are critical components.

Cartridges/syringes can be single-use or multi-use.

The stability of the formulation within the cartridge/syringe should be studied. It should be assured that the storage of the cartridge and number of re-uses, if applicable, have no impact on the stability of the finished product during shelf-life. In case of multiple uses, the physical-chemical and microbiological stability, before and after opening, should be investigated by:

- In-use studies reflecting the intended use of the cartridge (e.g. number of re-uses, storage conditions).
- Thermal cycling studies to ensure that the formulation can withstand temperature changes sustained by the cartridge each time it is heated for printing, if applicable.
- Appropriate rheological studies and texture analysis to evaluate the rheological behaviour and extrudability profile upon multiple uses.

In case of a suspension or a dry mixture, which may be prone to segregation during storage and transportation, the homogeneity of the formulation should be evaluated during development and confirmed by process validation and stability studies to ensure the correct dose delivery during printing. These studies should include assessment of multiple uses of the cartridges/syringes, if applicable.

The selection, optimisation and control of the 3DP process are also important aspects of the pharmaceutical development. The active substance(s) can be subject to different stresses depending on the technique used. This, in turn, can have an impact on the impurity profile of the product according to the active substance structure and properties. Therefore, during development it is important to consider the critical formulation attributes (e.g. stability of the formulation, solubilised or dispersed active substance in the formulation) together with the available manufacturing process options, in order to justify the selection of the 3DP process and confirm its appropriateness.
When developing a 3DP manufacturing process and its control strategy, it is important to consider the characteristics of the equipment that can affect process performance.

The manufacturing process development should consider equipment design and configuration, and identify the critical process parameters (CPPs) that should be monitored or controlled to ensure that the finished product is of the desired quality, e.g. depending on the technology used, the CPPs influencing the accuracy of the deposition may include, but are not limited to:

- Design of the nozzle (e.g. diameter, shape).
- Temperature (e.g. printing head, printing bed and chamber temperature).
- Pressure of extrusion.
- Speed of printing.
- Jetting frequency (for drop on demand inkjet printing).

Quality by Design (QbD) principles are well-suited for 3DP. These principles could be implemented in the development of formulations through thorough characterisation of the pharma ink, and in the development of the printing process through establishment of a design space. A good understanding of the properties of the raw materials, CPPs, finished product CQAs and their inter-relationships, is the starting point of manufacturing process qualification (see for further reference the ICH guideline Q8 (R2), and the EMA Questions and answers: Improving the understanding of NORs, PARs, DSp and normal variability of process parameters).

Process Validation
The process validation should be performed in accordance with the EMA Guideline on process validation for finished products (see references below). As a process involving new technologies, 3DP should be considered as a non-standard manufacturing process, in line with Annex II of that guideline. The process validation should be conducted with the printer which is intended to be used for routine commercial production. When technical changes are made to the equipment, the relevance of previous validation studies should be evaluated, and the level of re-validation studies required should be determined by appropriate risk analysis. In case the validation is carried out at the level of the ink manufacturer/printer supplier and the technology is transferred to the end user, the end user should demonstrate the robustness and reproducibility of the process by manufacturing a justified number of confirmatory batches (see question on GMP requirements for further guidance).
One specific feature of the 3DP process is the capacity of agilely producing a range of strengths from the same formulation, using a range of process parameters or conditions as per the validated printing design space. When several pre-defined dosage strengths (series of strengths) are applied for, a matrixing or bracketing approach may be acceptable for 3DP process validation, focusing on certain pre-determined and justified strengths. This is also valid for finished product stability studies (see for further reference ICH Q1D, VICH GL45 and EMA guideline on process validation).

Control Strategy
A control strategy should be established to ensure consistent quality, safety, and efficacy of the product. In particular, the applicant/manufacturer should justify the proposed control strategy approaches for in-process control testing and for release of the pharma ink and the finished product. The following points should be considered:
- Specifications for release and shelf-life for the pharma ink and the finished product should be proposed in compliance with relevant EMA guidelines and EP monographs, if applicable.

• The specification tests of the medicinal products manufactured by 3DP are, in general, the same as of the traditional solid oral pharmaceutical forms, e.g. assay, content uniformity, impurities, residual solvents, microbiological quality, disintegration and/or dissolution (see for further reference ICH Q6A and VICH GL39).

• The use of non-destructive techniques such as NIR and Raman spectroscopy during the manufacturing process should be considered, especially for small batch sizes with limited testing capacity. The control capability of the 3D printers (e.g. with pressure sensors for mass control, balance, NIR and Raman) could be used to monitor the printing process and discard non conforming dosage units in real-time.

• Based on the data collected during the manufacturing process, an appropriate combination of equipment design and configuration and CPPs, together with pre-defined material attributes, may provide greater assurance of product quality than end-product testing and, as such, be an integral part of the control strategy (see for further reference EMA Guidelines on Real Time Release Testing and Parametric Release).

4. What GMP requirements are relevant and applicable to support the use of 3DP in pharmaceutical manufacturing?

The 3DP manufacturing process generally consists of the following activities:
• Equipment design/qualification/validation (including 3D printing software).
• Manufacture of the intermediate cartridges/syringes.
• Printing process, including process control.
• Quality control testing.
• Batch certification and release.

Equipment
The 3D printer, including the computerised systems, as for any other manufacturing equipment, should be designed, located, qualified and maintained to suit its intended purpose in accordance with EU GMP (see for further reference EU GMP Chapter 3, Annexes 11 and 15, and Commission Implementing Regulation 2025/2091 Chapter IV, and Annexes IV and V).
A program of maintenance/calibration is required to ensure the good performance of the 3D printer, and this should be in line with the recommendations by the 3D printer manufacturer. In turn, the finished product manufacturer should ensure that the maintenance program is performed. In the event that maintenance activities are outsourced to the 3D printer manufacturer, a contract agreement detailing the respective responsibilities should be in place.
A preventive maintenance plan should be established to ensure optimal condition of use and the smooth operation of the 3D printer, and avoid unintentional deviations, equipment malfunctions and production interruptions. Monitoring systems must be in place to detect and resolve potential issues quickly.

Pharmaceutical materials (Cartridges/Syringes)
Usually, for 3DP, the pharmaceutical materials (active substances, excipients, or their mixtures) are presented in cartridges or syringes.
Cartridges/syringes can be manufactured directly by the finished product manufacturer conducting the 3D printing or received ready-to-use from a different manufacturer. The preparation of the active substance(s)/excipient(s) mixture and its filling into the cartridge are considered part of the finished product manufacturing process (intermediate manufacturing), and compliance with Part I of EU GMP guidelines and Commission Implementing Regulation 2025/2091 for products is required by any manufacturer conducting this activity (see references below).
The selection, qualification, approval and monitoring of suppliers of active substances, excipients, starting materials or pharmaceutical containers should be performed according to the EU GMP (see for further reference the Chapters 4, 5 and 7 of the EU GMP, and Chapters V, VI and IX of the Commission Implementing Regulation 2025/2091), and the level of supervision should be proportionate to the risks posed by the individual materials, taking into account of their source, manufacturing process, supply chain complexity and the final use to which the material is put in the medicinal product.

Manufacturing process
The amount of information received from the manufacturer of the 3D printer should be sufficient for the medicinal product manufacturer to fully understand the functioning of the equipment and to

identify the process parameters critical for the product.
The application of quality risk management (QRM) to the 3D printing process can help to proactively identify and control potential quality issues, and to ensure the expected quality of the 3D printed products is delivered to the patients. QRM should be integrated into existing operations and documented appropriately (see for further reference ICH Q9 R1).

The high accuracy of deposition (resolution) is an inherent feature of 3DP technology, which is an advantage over other traditional manufacturing methods. The defined process parameters should be monitored and, where necessary, controlled to ensure the process produces products with the desired quality within the validated ranges (see also the pharmaceutical development paragraph in question on quality requirements above for further details).

At every stage of manufacturing, products and materials should be protected from microbial and other contamination, including cross-contamination. It should be prevented by appropriate design and maintenance of the premises and equipment, and use of cleaning procedures of validated effectiveness. Risk minimization measures should be proposed, such as the use of disposable material in contact with the product. Dedicated premises or containment may be necessary, according to the QRM, in case of highly active components, toxic or sensitizing materials handling.
Appropriate training should be provided for the personnel according to Chapter 2 of the EU GMP and Chapter III of the Commission Implementing Regulation 2025/2091, considering also the involvement of the 3D printer manufacturer in the personnel training, e.g. file conversions maintenance, equipment uses.
Outsourced activities should be appropriately defined, agreed and controlled, according to Chapter 7 of the EU GMP and the Chapter IX of the Commission Implementing Regulation 2025/2091, to ensure the outsourced activities are carried out successfully, e.g. 3D printer manufacturer qualification, maintenance, software update, and modifications to the equipment.

Qualification and validation
It is a GMP requirement that pharmaceutical product manufacturers control the critical aspects of their particular operations through qualification and validation over the life cycle of the product and process (see for further reference Annex 15 of EU GMP guidelines and the Annex V of the Commission Implementing Regulation 2025/2091). Use of QRM should ensure that the manufacturer's efforts are focused on the areas of highest risk by addressing CPPs and potential failure modes.
It is expected that the 3D printing process (e.g. printing parameters of speeds, temperatures) is validated. The 3D printer, if used to manufacture medicinal products, should be considered pharmaceutical production equipment and should be adequately qualified. Both qualification and validation activities should be completed in accordance with annex 15 of EU GMP guidelines and Annex V of the Commission Implementing Regulation 2025/2091 (see references below).
The 3D printing equipment should be used within the recommended settings/conditions of its manufacturer/supplier, unless the in-house operating mode has been fully validated. It is acceptable that 3D printer qualification activities are carried out by the manufacturer/supplier of the printer. Equipment knowledge and understanding from the 3D printer manufacturer are also important for the finished product manufacturer/user for building their own knowledge to support the equipment and process validation and demonstrate that the printing process is capable of consistently producing medicinal products that meet pre-determined quality and performance standards. The collaboration between the users and the pharma ink/printer suppliers is considered also relevant in the case of PAT tools implementation. In the event that qualification/validation activities are outsourced to the 3D printer manufacturer, a contract agreement should be in place (see for further reference Chapter 7 of the EU GMP and the Chapter IX of the Commission Implementing Regulation 2025/2091).
The 3D printer should be cleaned and decontaminated depending on the products being manufactured. The related cleaning processes should be validated, and appropriate procedures should be established. The cleaning of the empty cartridges/syringes should also be validated (see for further reference Chapter 4 and Annex 15 of the EU GMP, and the Chapter V and Annex V of the Commission Implementing Regulation 2025/2091). The use of dedicated/single-use cartridges/syringes could reduce risks of contamination.

A 3D printer is a fully computer-driven system, and compatibility between printer and software is critical to the quality of the final medicinal product. The computer validation should be carried out according to the Annex 11 of the EU GMP guidelines and the annex V of the Commission Implementing Regulation 2025/2091 (see references below), and should include, among others, data integrity management, 3D model design, qualification and validation, qualification of the file transfer to the

printer, software validation and software update management. In case Artificial Intelligence (AI) is used in the 3DP, the Annex 22 of the EU GMP guidelines and the EMA Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle should be considered (see references below).

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5. References

EMA Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (EMA/CHMP/QWP/545525/2017 Rev. 2)
ICH guideline Q8 (R2) on pharmaceutical development (EMA/CHMP/ICH/167068/2004)
ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
VICH GL39 Test procedures and acceptance criteria for new veterinary drug substances and new medicinal products
ICH guideline Q9 (R1) on quality risk management
ICH: Q 1 D: Bracketing and matrixing designs for stability testing of drug substances and drug products
VICH GL 45 Quality: Bracketing and matrixing designs for stability testing of new veterinary drug substances and medicinal products vich-gl-45-quality-bracketing-and-matrixing-designs-stability testing-new-veterinary-drug-substances-and-medicinal-products_en.pdf
EMA Questions and answers: Improving the understanding of NORs, PARs, DSp and normal variability of process parameters (EMA/CHMP/CVMP/QWP/354895/2017)

EMA Guideline on process validation for finished products - information and data to be provided in regulatory submissions (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1)
EMA Guideline on Real Time Release Testing (formerly Guideline on Parametric Release) (EMA/CHMP/QWP/811210/2009-Rev1)
EMA Guideline on Parametric release (EMA/CVMP/QWP/339588/2005 – Rev 1)
EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines
Commission Implementing Regulation (EU) 2025/2091 of 17 October 2025 laying down good manufacturing practice for veterinary medicinal products in accordance with Regulation (EU) 2019/6 of the European Parliament and of the Council
Commission Implementing Regulation (EU) 2025/2154 of 17 October 2025 laying down good manufacturing practice for active substances used as starting materials in veterinary medicinal products in accordance with Regulation (EU) 2019/6 of the European Parliament and of the Council:
EMA Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle:

1.1.22 General GMP

1. What are the differences between EU and World Health Organization (WHO) requirements for GMP? H July 2006

EU GMP principles and guidelines are laid down in Directive 2003/94/EC (human medicines) and Directive 91/412/EEC (veterinary products). These principles and guidelines are subject to further detailed guidance in the form of the EU GMP guideline with its annexes.

WHO publishes its own GMP guidance documents.

Although EU and WHO GMP guidance documents do differ in some details, the main principles remain the same. EU requirements fulfil all the recommendations of WHO.

1.1.23 GMP certificates, non-compliance statements and manufacturing authorisations

1. Since Manufacturing Authorisations and GMP certificates are uploaded into the EudraGMDP database do I need a paper copy in order to support regulatory submissions? April 2017

Documents appearing in the EudraGMDP database are uploaded by the national competent authorities through a secure network guaranteeing their authenticity.For submissions to EU authorities paper documents are not required as a reference can be made to the EudraGMDP database.

EU authorities are aware that these documents are also used to support regulatory submissions in third countries and that various additional requirements, including apostilled copies are sometimes expected. In view of the integrity of entries in the EudraGMDP database, EU authorities strongly encourage reliance on the database.

Any concerns about a certificate/authorisation in the database should be addressed to the issuing authority.

A **GMP certificate** is a certificate issued following a GMP inspection, by the competent authority responsible for carrying out the inspection, to confirm the GMP compliance status of the inspected site.

2. What is a GMP certificate, what is the difference between GMP certificates, certificates of medicinal product, also called certificates of pharmaceutical products, & certificates of suitability to the monographs of European Pharmacopoeia?H+V Jul 2006

GMP certificates are site-specific, but can be restricted to particular activities depending on the scope of the inspection (e.g., manufacturing activities related to a specific product). Directives 2001/82/EC and 2001/83/EC, as amended state that after every GMP inspection, and within 90 days of the inspection, a GMP certificate shall be issued to a manufacturer, if the outcome of the inspection shows that the manufacturer complies with GMP.

CMPs are product-specific certificates issued by the competent authority that granted the marketing authorisation. The European Medicines Agency issues CMPs on behalf of the European Commission for centrally authorised products.

CMPs are issued in the context of the World Health Organization certification scheme on the quality of pharmaceutical products moving in international commerce, to confirm the marketing-authorisation status of the products. These certificates also confirm the GMP compliance status of the manufacturing sites. CMPs are mainly used by companies to support applications to export their pharmaceutical products to countries with less-developed regulatory systems.

CEPs are certificates issued by the European Directorate for the Quality of Medicines and Healthcare (EDQM) to confirm that a certain active substance is produced according to the requirements of the relevant monograph of the European Pharmacopoeia or of the monograph on transmission spongiform encephalopathies.

CEPs can be used by companies when submitting an application for marketing authorisation, and replace much of the documentation required for the active substance in the marketing-authorisation dossier. GMP inspections of active-substance manufacturers can be requested by EDQM in the context of the CEP certification scheme.

3. Does the Agency issue GMP certificates? H+V July 2006

No, the competent authority responsible for carrying out the inspection issues the GMP certificate, or makes an entry of non-compliance into the EudraGMP database.

4. Which EU and EEA authorities conduct mutually recognised inspections and issue GMP certificates? H+V November 2011

All EU and EEA national competent authorities conducting inspections are obliged to enter GMP certificates in the EudraGMP database. Hence, any GMP certificate appearing in the database is mutually recognised and the database authenticates the certificate.

If a certificate cannot be found in the database, the issuing authority should be contacted.

5. How can a GMP non-compliance statement be lifted? September 2017

In principle, a GMP non-compliance statement can only be lifted following a new inspection by an EU authority that results in the issue of a GMP certificate. In practice, this can present difficulties for manufacturers located in third countries.

For sites located in third countries the GMP non-compliance statement may mean that the site is no longer listed in marketing authorisations or applications and therefore there will be no reason for a new EU inspection. However, EU inspectorates acknowledge that the manufacturer may subsequently take remedial measures to bring the site into an acceptable level of compliance. As there is no intention to convey that the site continues to operate to an unacceptable level of non-compliance and given the absence of a new

inspection trigger, the issuing authority will add a clarifying remark where a non-compliance statement appears in EudraGMDP over a prolonged period of time.

1.1.24 Inspection coordination

1. Does the Agency perform GMP inspections? H+V July 2006

The Agency does not perform inspections. They are carried out on its behalf by the national competent authorities of the member states of the EEA, in connection with products under the centralised marketing-authorisation procedure.

2. If a site in a third country has plans to export products to the EEA, is it possible to apply for a GMP inspection on a voluntary basis? H+V July 2006

Normally, the need for inspection under these circumstances is triggered by an application for a marketing authorisation. It may be possible to request an inspection on a voluntary basis, but as the competent authorities will have other priorities, there is no guarantee that such a request will be met.

To explore this possibility, the authorities of the Member State into which the product will be imported into the EEA should be approached. In any case, applicants are encouraged to approach the relevant authority in advance of submission in order to facilitate third-country inspection planning.

3. When a new application is submitted in the EEA and a GMP inspection is deemed necessary, which competent authority carries out the inspection? H+V July 2006

If the site is located in the EEA, the competent authority of the Member State where the site is located carries out the inspection.

For sites located in countries outside the EEA, the responsible authority for inspection (the 'supervisory authority') is the authority in whose territory the importing site is located. If the supervisory authority is not able to carry out the inspection for any reason, it can be delegated to another EEA competent authority.

If there is a mutual recognition agreement (MRA) in place between the countries where the site is located and the European Community, the results of GMP inspections carried out by the MRA partner authority are normally recognised by the EU authorities.

1.1.25 Data integrity

Data integrity enables good decision-making by pharmaceutical manufacturers and regulatory authorities.It is a fundamental requirement of the pharmaceutical quality system described in EU GMP chapter 1, applying equally to manual (paper) and electronic systems.

Promotion of a quality culture together with implementation of organisational and technical measures which ensure data integrity is the responsibility of senior management. It requires participation and commitment by staff at all levels within the company, by the company's suppliers and by its distributors.

Senior management should ensure that data integrity risk is assessed, mitigated and communicated in accordance with the principles of quality risk management. The effort and resource assigned to data integrity measures should be commensurate with the risk to product quality, and balanced with other quality assurance resource demands. Where long term measures are identified in order to achieve the desired state of control, interim measures should be implemented to mitigate risk, and should be monitored for effectiveness.

The following questions and answers describe foundational principles which facilitate successful implementation of existing guidance published by regulatory authorities participating in the PIC/S scheme. It should be read in conjunction with national guidance, medicines legislation and the GMP standards published in Eudralex volume 4.

The importance of data integrity to quality assurance and public health protection should be included in personnel training programmes.

- WHO - Annex 5: guidance on good data and record management practices

1. How can data risk be assessed?

Data risk assessment should consider the vulnerability of data to involuntary or deliberate amendment, deletion or recreation. Control measures which prevent unauthorised activity and increase visibility / detectability can be used as risk mitigating actions.

Examples of factors which can increase risk of data integrity failure include complex, inconsistent processes with open-ended and subjective outcomes. Simple tasks which are consistent, well-defined and objective lead to reduced risk.

Risk assessment should include a business process focus (e.g. production, QC) and not just consider IT system functionality or complexity. Factors to consider include:

- Process complexity
- Process consistency, degree of automation /human interface
- Subjectivity of outcome / result
- Is the process open-ended or well defined

This ensures that manual interfaces with IT systems are considered in the risk assessment process. Computerised system validation in isolation may not result in low data integrity risk, in particular when the user is able to influence the reporting of data from the validated system.

2. How can data criticality be assessed?

The decision which data influences may differ in importance, and the impact of the data to a decision may also vary. Points to consider regarding data criticality include:

- What decision does the data influence?

For example: when making a batch release decision, data which determines compliance with critical quality attributes is of greater importance than warehouse cleaning records.

- What is the impact of the data to product quality or safety?

For example: for an oral tablet, active substance assay data is of greater impact to product quality and safety than tablet dimensions' data.

3. What does Data Lifecycle refer to?

'Data lifecycle' refers to how data is generated, processed, reported, checked, used for decision-making, stored and finally discarded at the end of the retention period.

Data relating to a product or process may cross various boundaries within the lifecycle, for example:

- IT systems
    - Quality system applications
    - Production
    - Analytical
    - Stock management systems
    - Data storage (back-up and archival)
- Organisational
    - Internal (e.g. between production, QC and QA)
    - External (e.g. between contract givers and acceptors)

- Cloud-based applications and storage

4. Why is Data lifecycle management important to ensure effective data integrity measures?

Data integrity can be affected at any stage in the lifecycle. It is therefore important to understand the lifecycle elements for each type of data or record, and ensure controls which are proportionate to data criticality and risk at all stages.

5. What should be considered when reviewing the Data lifecycle?

The 'Data lifecycle' refers to the:

- Generation and recording of data
- Processing into usable information
- Checking the completeness and accuracy of reported data and processed information
- Data (or results) are used to make a decision
- Retaining and retrieval of data which protects it from loss or unauthorised amendment
- Retiring or disposal of data in a controlled manner at the end of its life

'Data Lifecycle' reviews are applicable to both paper and electronic records, although control measures may be applied differently. In the case of computerised systems, the 'data lifecycle' review should be performed by business process owners (e.g. production, QC) in collaboration with IT personnel who understand the system architecture. The description of computerised systems required by EU GMP Annex 11 paragraph 4.3 can assist this review. The application of critical thinking skills is important to not only identify gaps in data governance, but to also challenge the effectiveness of the procedural and systematic controls in place.

Segregation of duties between data lifecycle stages provides safeguards against data integrity failure by reducing the opportunity for an individual to alter, misrepresent or falsify data without detection.

Data risk should be considered at each stage of the data lifecycle review.

6. Data lifecycle: What risks should be considered when assessing the generating and recording of data?

The following aspects should be considered when determining risk and control measures:

- How and where is original data created (i.e. paper or electronic)
- What metadata is associated with the data, to ensure a complete, accurate and traceable record, taking into account ALCOA principles. Does the record permit the reconstruction of the activity
- Where is the data and metadata located
- Does the system require that data is saved to permanent memory at the time of recording, or is it held in a temporary buffer

In the case of some computerised analytical and manufacturing equipment, data may be stored as a temporary local file prior to transfer to a permanent storage location (e.g. server). During the period of 'temporary' storage, there is often limited audit trail provision amending, deleting or recreating data. This is a data integrity risk. Removing the use of temporary memory (or reducing the time period that data is stored in temporary memory) reduces the risk of undetected data manipulation.

- Is it possible to recreate, amend or delete original data and metadata;

Controls over paper records are discussed elsewhere in this guidance.

Computerised system controls may be more complex, including setting of user privileges and system configuration to limit or prevent access to amend data. It is important to review all data access opportunities, including IT helpdesk staff, who may make changes at the request of the data user. These changes should be procedurally controlled, visible and approved within the quality system.

- How data is transferred to other locations or systems for processing or storage;

Data should be protected from possibility of intentional or unintentional loss or amendment during transfer to other systems (e.g. for processing, review or storage). Paper records should be protected from amendment, or substitution. Electronic interfaces should be validated to demonstrate security and no corruption of data, particularly where systems require an interface to present data in a different structure or file format.

Does the person processing the data have the ability to influence what data is reported, or how it is presented.

7. Data lifecycle: What risks should be considered when assessing the processing data into usable information?

The following aspects should be considered when determining risk and control measures:

- How is data processed;

Data processing methods should be approved, identifiable and version controlled. In the case of electronic data processing, methods should be locked where appropriate to prevent unauthorised amendment.

- How is data processing recorded;

The processing method should be recorded. In situations where raw data has been processed more than once, each iteration (including method and result) should be available to the data checker for verification.

- Does the person processing the data have the ability to influence what data is reported, or how it is presented;

Even 'validated systems' which do not permit the user to make any changes to data may be at risk if the user can choose what data is printed, reported or transferred for processing. This includes performing the activity multiple times as separate events and reporting a desired outcome from one of these repeats.

Data presentation (e.g. changing scale of graphical reports to enhance or reduce presentation of analytical peaks) can also influence decision making, and therefore impact data integrity.

8. Data lifecycle: What risks should be considered when checking the completeness and accuracy of reported data and processed information?

The following aspects should be considered when determining risk and control measures:

- Is original data (including the original data format) available for checking;

The format of the original data (electronic or paper) should be preserved, and available to the data reviewer in a manner which permits interaction with the data (e.g. search, query). This approach facilitates a risk-based review of the record, and can also reduce administrative burden for instance utilising validated audit trail 'exception reports' instead of an onerous line-by-line review.

- Are there any periods of time when data is not audit trailed;

This may present opportunity for data amendment which is not subsequently visible to the data reviewer. Additional control measures should be implemented to reduce risk of undisclosed data manipulation.

- Does the data reviewer have visibility and access to all data generated;

This should include any data from failed or aborted activities, discrepant or unusual data which has been excluded from processing or the final decision-making process. Visibility of all data provides protection against selective data reporting or 'testing into compliance'.

- Does the data reviewer have visibility and access to all processing of data;

This ensures that the final result obtained from raw data is based on good science, and that any data exclusion or changes to processing method is based on good science. Visibility of all processing information provides protection against undisclosed 'processing into compliance'.

The following aspects should be considered when determining risk and control measures:

- When is the pass / fail decision taken;

If data acceptability decisions are taken before a record (raw data or processed result) is saved to permanent memory, there may be opportunity for the user to manipulate data to provide a satisfactory result, without this change being visible in audit trail. This would not be visible to the data reviewer.

This is a particular consideration where computerised systems alert the user to an out of specification entry before the data entry process is complete (i.e. the user 'saves' the data entry), or saves the record in temporary memory.

9. Data lifecycle: What risks should be considered when data (or results) are used to make a decision?

10. Data lifecycle: What risks should be considered when retaining and retrieving data to protect it from loss or unauthorised amendment?

The following aspects should be considered when determining risk and control measures:

- How / where is data stored;

Storage of data (paper or electronic) should be at secure locations, with access limited to authorised persons. The storage location must provide adequate protection from damage due to water, fire, etc.

- What are the measures protecting against loss or unauthorised amendment;

Data security measures should be at least equivalent to those applied during the earlier Data lifecycle stages. Retrospective data amendment (e.g. via IT helpdesk or data base amendments) should be controlled by the pharmaceutical quality system, with appropriate segregation of duties and approval processes.

- Is data backed up in a manner permitting reconstruction of the activity;

Back-up arrangements should be validated to demonstrate the ability to restore data following IT system failure. In situations where metadata (including relevant operating system event logs) are stored in different file locations from raw data, the back-up process should be carefully designed to ensure that all data required to reconstruct a record is included.

Similarly, 'true copies' of paper records may be duplicated on paper, microfilm, or electronically, and stored in a separate location.

- What are ownership / retrieval arrangements, particularly considering outsourced activities or data storage;

A technical agreement should be in place which addresses the requirements of Part I Chapter 7 and Part II Section 16 of the GMP guide.

11. Data lifecycle: What risks should be considered when retiring or disposal of data in a controlled manner at the end of its life?

The following aspects should be considered when determining risk and control measures:

- The data retention period

This will be influenced by regulatory requirements and data criticality. When considering data for a single product, there may be different data retention needs for pivotal trial data and manufacturing process / analytical validation data compared to routine commercial batch data.

- How data disposal is authorised

Any disposal of data should be approved within the quality system and be performed in accordance with a procedure to ensure compliance with the required data retention period.

12. Is it required by the EU GMP to implement a specific procedure for data integrity?

There is no requirement for a specific procedure, however it may be beneficial to provide a summary document which outlines the organisations total approach to data governance.

A compliant pharmaceutical quality system generates and assesses a significant amount of data. While all data has an overall influence on GMP compliance, different data will have different levels of impact to product quality.

A quality-risk management (ICH Q9) approach to data integrity can be achieved by considering data risk and data criticality at each stage in the Data lifecycle. The effort applied to control measures should be commensurate with this data risk and criticality assessment.

The approach to risk identification, mitigation, review and communication should be iterative, and integrated into the pharmaceutical quality system. This should provide senior management supervision and permit a balance between data integrity and general GMP priorities in line with the principles of ICH Q9 & Q10.

13. How are the data integrity expectations (ALCOA) for the pharmaceutical industry prescribed in the existing EU GMP relating to active substances and dosage forms published in Eudralex volume 4?

The main regulatory expectation for data integrity is to comply with the requirement of ALCOA principles. The table below provide for each ALCOA principle the link to EU GMP references (Part I, Part II and Annex 11):

	Basic Requirements for Medicinal Products (Part I): Chapter 4[1] / Chapter 6[2]	Basic Requirements for Active Substances used as Starting Materials (Part II) : Chapter 5[3] / Chapter 6[4]	Annex 11 (Computerised System)
Attributable (data can be assigned to the individual performing the task)	[4.20, c & f], [4.21, c & i], [4.29, e]	[6.14], [6.18], [6.52]	[2], [12.4], [15]
Legible (data can be read by eye or electronically and retained in a permanent format)	[4.1], [4.2], [4.7], [4.8], [4.9], [4.10]	[5.43] [6.11], [6.14], [6.15], [6.50]	[7.1], [9], [10], [17]
Contemporaneous (data is created at the time the activity is performed)	[4.8]	[6.14]	[12.4], [14]
Original (data is in the same format as it was initially generated, or as a 'verified copy', which retains content and meaning)	[4.9], [4.27], [Paragraph "Record"]	[6.14], [6.15], [6.16]	[8.2], [9]
Accurate (data is true / reflective of the activity or measurement performed)	[4.1], [6.17]	[5.40], [5.45], [6.6]	[Paragraph "Principles"], [5], [6], [10], [11]

[1]Chapter 4 (Part I): Documentation
[2]Chapter 6 (Part I): Quality control
[3]Chapter 5 (Part II): Process equipment (computerized system)
[4]Chapter 6 (Part II): Documentation and records

14. How should the company design and control their paper documentation system to prevent the unauthorised re-creation of GMP data?

The template (blank) forms used for manual recordings may be created in an electronic system (Word, Excel, etc.). The corresponding master documents should be approved and controlled electronically or in paper versions. The following expectations should be considered for the template (blank) form:

- have a unique reference number (including version number) and include reference to corresponding SOP number
- should be stored in a manner which ensures appropriate version control
- if signed electronically, should use a secure e-signature

The distribution of template records (e.g. 'blank' forms) should be controlled. The following expectations should be considered where appropriate, based on data risk and criticality:

- enable traceability for issuance of the blank form by using a bound logbook with numbered pages or other appropriate system. For loose leaf template forms, the distribution date, a sequential issuing number, the number of the copies distributed, the department name where the blank forms are distributed, etc. should be known
- Distributed copies should be designed to avoid photocoping either by using a secure stamp, or by the use of paper colour code not available in the working areas or another appropriate system.

15. What controls should be in place to ensure original electronic data is preserved?

Computerised systems should be designed in a way that ensures compliance with the principles of data integrity. The system design should make provisions such that original data cannot be deleted and for the retention of audit trails reflecting changes made to original data.

16. Why is it important to review electronic data?

In the case of data generated from an electronic system, electronic data is the original record which must be reviewed and evaluated prior to making batch release decisions and other decisions relating to GMP related activities (e.g. approval of stability results, analytical method validation etc.). In the event that the review is based solely on printouts there is potential for records to be excluded from the review process which may contain un-investigated out of specification data or other data anomalies. The review of the raw electronic data should mitigate risk and enable detection of data deletion, amendment, duplication, reusing and fabrication which are common data integrity failures.

Example of an inspection citing:

Raw data for HPLC/GC runs which had been invalidated was stored separately to the QC raw data packages and had not been included in the review process.

In the above situation, the procedure for review of chromatographic data packages did not require a review of the electronic raw data or a review of relevant audit trails associated with the analyses. This lead to the exclusion of records from the review process and to lack of visibility of changes made during the processing and reporting of the data. The company was unable to provide any explanation for the data which had been invalidated.

17. Is a risk-based review of electronic data acceptable?

Yes. The principles of quality risk management may be applied during the review of electronic data and review by exception is permitted, when scientifically justified.

Exception Reporting is used commonly as a tool to focus the review of electronic data such as (but not limited to) electronic batch records. Exception reporting rapidly highlights to the reviewer one of the most critical elements of batch review, i.e. the exceptions. The level of review of the full electronic batch record can vary based on the exceptions as well as the level of confidence and experience with a particular process.

Appropriate testing and validation must be completed for the automated system and the output Batch Exception Report to ensure its functionality meets the business and regulatory requirements as per GMP.

18. What are the expectations for the self-inspection program related to data integrity?

Ongoing compliance with the company's data governance policy/procedures should be reviewed during self-inspection, to ensure that they remain effective. This may also include elements of the Data lifecycle discussed in Q3-Q9.

19. What are my company's responsibilities relating to data integrity for GMP activities contracted out to another company?

Data integrity requirements should be incorporated into the company's contractor/vendor qualification/assurance program and associated procedures.

In addition to having their own data governance systems, companies outsourcing activities should verify the adequacy of comparable systems at the contract acceptor. The contract acceptor should apply equivalent levels of control to those applied by the contract giver.

Formal assessment of the contract acceptors competency and compliance in this regard should be conducted in the first instance prior to the approval of a contractor, and thereafter verified on a periodic basis at an appropriate frequency based on risk.

20. How can a recipient (contract giver) build confidence in the validity of documents such as Certificate of Analysis (CoA) provided by a supplier (contract acceptor)?

The recipient should have knowledge of the systems and procedures implemented at the supplier for the generation of the CoA. Arrangements should be in place to ensure that significant changes to systems are notified and the effectiveness of these arrangements should be subjected to periodic review.

Data related to activities which are outsourced are routinely provided as summary data in a report format (e.g. CoA). These summary documents are reviewed on a routine basis by the contract acceptor and therefore the review of data integrity at the contract acceptor site on a regular periodic basis (e.g. during on-site audit) takes on even greater significance, in order to build and maintain confidence in the summary data provided.

21. What are the expectations in relation to contract calibration service providers who conduct calibrations on-site and/or off-site? Are audits of these companies premises required?

Using the principles of QRM to assess data criticality and risk, the company should include assessment of data governance systems implemented by the service provider when making decisions on service contracts. This may be achieved by on-site audit or desk-based assessment of information submitted by the service provider.

22. What is expected of my company in the event that one of my approved contractors is issued with a warning letter/statement of non-compliance concerning data integrity, from a regulatory authority?

What is expected of my company in the event that one of my approved contractors (e.g. **active substance** manufacturer, finished product manufacturer, quality control laboratory etc.) is issued with a warning letter/statement of non-compliance concerning data integrity, from a **regulatory authority**?

It is considered that the company should evaluate the risk to its products manufactured/released using the principles of quality risk management. Risk assessments should be made available to Inspectors, on request.

Depending on the outcome of the risk assessment, appropriate action should be taken which may entail delisting the contractor from the approved contractor list. In the event that abnormal disruption in supply may result from a contractor compliance situation, relevant regulatory authorities should be consulted in this regard.

23. Where does my company's responsibility begin and end in relation to data integrity aspects of the supply chain for medicinal products?

All actors in the supply chain play an important part in overall data integrity and assurance of product quality.

Data governance systems should be implemented from the manufacture of starting materials right through to the delivery of medicinal products to persons authorised or entitled to supply medicinal products to the public.

Relative responsibilities and boundaries should be documented in the contracts between the relevant parties. Final responsibility of ensuring compliance throughout the supply chain rests with batch certifying QP.

1.1.26 GDP requirements (Updated Jan 2023)

1. Is it acceptable that storage conditions are not monitored for medicinal products which do not have any predefined storage conditions on the outer packaging?

No. According to the Guideline on declaration of storage conditions, marketing authorisation holders have to provide **stability data** for storage conditions at 25°C / 60% relative humidity (RH), or 30°C / 65% RH (long term) and 40°C / 75% RH (accelerated), in order to justify not including a statement in the medicinal product labelling.

This stability data is generated according to the temperature and humidity conditions of climate zone I (temperate) and II (Mediterranean/subtropical) in Europe. For more information, see the World Health Organization Expert Committee on Specifications for Pharmaceutical Preparations forty-third report, Annex 2: Stability testing of active pharmaceutical ingredients and finished pharmaceutical products.

No labelling statement means that controls should be in place to maintain conditions relevant to climate zones I and II. Consequently, the **temperature should be monitored** during storage and transport. Appropriate limits should be set for temperature monitoring to ensure that product stability is not adversely affected.

2. May a broker have broker activities between parties outside the EEA? Jan 2023

No. The Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use state in paragraph 10.4 v): "procedure for verifying that their supplying wholesale distributors hold a distribution authorisation, their supplying manufacturers or importers hold a manufacturing authorisation and their customers are authorised to supply medicinal products in the Member State concerned".

That means that both suppliers and customers should be located in the EEA. Brokering activities regarding both supplier and customer located outside the EEA fall outside the scope of the EU legislation (GDP guidelines).

3. May a broker have broker activities for medicinal products without a marketing authorisation in the EEA (but with a marketing authorisation in a county outside the EEA)? Jan 2023

No. The Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use state in paragraph 10.4 iv): "procedure for ensuring that medicinal products brokered have a marketing authorisation".

That means that the medicinal products must have a marketing authorisation in at least one of the EEA member states.

4. Are remote activities by the RP (i.e. when not at the authorised site address specified on the WDA) allowed?

Remote activities could be allowed if accepted by the national competent authority where the authorised site is located. Some competent authorities may have specific requirements regarding this. Wholesalers and RPs should ensure that they comply with any applicable local requirements. In order to determine what requirements apply, wholesalers should consult with their national competent authority.

5. Where remote RP activities are allowed, what conditions should apply?

RP activities should take place within the EU/EEA (or Northern Ireland) in all cases.

1.1.27 Considerations for wholesale distributors/brokers on suspicious offers - Dec 2024

1. How will wholesale distributors and brokers know if they are given suspicious offers? (Dec 2024)

Wholesalers and others buying or receiving medicinal products must be aware of the risk that products offered to them are falsified, illegitimate or in other ways not of full quality. However, it is often difficult to unveil if an offer is suspicious.

Some guidance regarding suspicious offers may be understood from article 5.2 in the guidelines for European Union (EU) GDP guidelines for human medicinal products.

When entering into a new contract with new suppliers, the wholesale distributor should carry out 'due diligence' checks in order to assess the suitability, competence and reliability of the other party. Attention should be paid to:

- *(i) the reputation or reliability of the supplier;*
- *(ii) offers of medicinal products more likely to be falsified;*
- *(iii) large offers of medicinal products which are generally only available in limited quantities; and*
- *(iv) out-of-range prices.*

Similar guidance is given in regulation for European Union (EU) GDP regulation for veterinary medicinal products in article 21.2.

When entering into a contract with new suppliers, the persons referred to in Article 1(2) shall carry out so called due diligence checks in order to assess the suitability, competence and reliability of the other party. The due diligence checks shall consider:

- *(a) the reputation or reliability of the supplier;*
- *(b) offers of veterinary medicinal products more likely to be falsified;*
- *(c) large offers of veterinary medicinal products which are generally only available in limited quantities;*
- *(d) unusually high diversity of veterinary medicinal products handled by supplier;*
- *(e) abnormally low prices.*

Additionally, a buyer of medicinal products may consider the following aspects. Offers corresponding to the points below may be suspicious.

- Offers of highly demanded medicinal products, e.g. products in supply shortages.
- Offers communicated through chat apps or unconventional channels – WhatsApp, Telegram, Facebook and similar.
- The urgency of the offer. Offers given with a very short time to reply.
- Pictures of the product in offers, where the Unique Identifiers ("2D code") indicates that the pack is decommissioned, or the tamper evident function is broken.
- Offers being made by brokers or wholesalers, manufacturers or importers which are not listed in the EudraGMDP database (for wholesalers, manufacturers or importers) or official repository held by a national competent authority (for brokers).
- Offers where the supplier does not yet have the products at hand but allege that it will be available at a later time.
- Offers of medicinal product that are unexpected from an economic perspective, e.g. high price country selling to low price country.
- Offers of medicinal products that are unexpected from a language or geographical perspective, e.g. a wholesaler in one member state offering, to another member state, packages having the target country's labelling.

To verify a wholesalers identity, use the EudraGMDP database. To verify a brokers identity use the repositories indicated through links to NCAs provided by HMA.

Article 5.2 in the GDP guidelines for human medicinal products states the following:

Wholesale distributors must obtain their supplies of medicinal products only from persons who are themselves in possession of a wholesale distribution authorisation, or who are in possession of a manufacturing authorisation which covers the product in question (Article 80(b) of Directive 2001/83/EC).

Article 101 of regulation (EU) 2019/6 for veterinary medicinal products states that *wholesale distributors shall obtain veterinary medicinal products only from holders of a manufacturing authorisation or from other holders of a wholesale distribution authorisation.*

Wholesale distributors receiving medicinal products from third countries for the purpose of importation, i.e. for the purpose of placing these products on the EU market, must hold a manufacturing authorisation (Article 40(3) of Directive 2001/83/EC and article 88 (1c) regulation 2019/6).

Even if it is not mentioned explicitly, this prohibits the supply of medicinal products from pharmacies (or others supplying medicinal products to the public) to wholesalers, except for returns described in 6.3(ii) of the human GDP Guideline or article 30(c) of the veterinary GDP regulations, i.e. return of medicinal products from a pharmacy to the wholesaler that supplied the product.

2. What should wholesale distributors and brokers do if they learn of suspicious offers? (Dec 2024)

Any wholesale distributor or broker who learns of a substantiated suspicious offer should immediately contact the national competent authority as well as the marketing authorisation holder.

This follows from articles 5.1, 6.1, 6.4, 10.2, 10.4 of European Union (EU) GDP guidelines for human medicinal products, and articles 10.3 18.1 (m), 20.1, 31 in regulation (EU) 2021/1248 on wholesaler of veterinary medicinal products.

The distributor or broker should contact the authorities and marketing authorisation holder regardless if they are themselves being offered suspected falsified products, or if they learn of suspected offers being made to others, e.g. when verifying unique identifiers of packs on behalf of another actor.

1.1.28 Art. 23 (3) of regulation 2021/1248 requirement relating the nature of check at the reception of veterinary medicinal products before being transferred to saleable stock

1. What kind of proof of release to the market could be requested and controlled by the staff of WDA holder for ensuring that received veterinary medicinal products coming from another Member State be transferred to saleable stock? (Oct. 2022)

Wholesalers shall ensure first that all veterinary medicinal products they distribute in the Union are covered by a marketing authorisation, a registration or another kind of authorisation (parallel trade, importation authorisation…). In addition, they shall ensure that veterinary medicinal products intended for the EU and EEA countries should not be transferred to saleable stock before assurance has been obtained that they are authorised for sale.

According to article 97 of Regulation 2019/6, the Qualified person responsible for manufacturing and batch release shall draw up a control report establishing that each batch of the veterinary medicinal products is manufactured in compliance with good manufacturing practice, and tested in compliance with the terms of the marketing authorisation. Such control reports shall be valid throughout the Union.

Batches of veterinary medicinal products which have undergone the controls referred to in Art. 97 of regulation 2019/6 in a Member State are exempt from the controls in another Member State where they will be marketed if they are accompanied by the control reports signed by the qualified person.

In this context, wholesalers shall check that batches of veterinary medicinal products coming from another member state are be accompanied by evidence that the manufacturer's qualified person has certified the finished product batch. This check could be done by different means : paper based check (copy of controls reports), electronically check or other equivalent system as agreed with the supplier (manufacturer or wholesaler).

1.1.29 Active substance registration

1. What are the registration requirements for manufacturers and importers of active substances used in medicinal products for human use?

The requirements for registration of manufacturers and importers of active substances (and active substance intermediates, i.e crude active substances or other active substance intermediates, the manufacturing of which is described in a regulatory dossier) as required under Article 52a of Directive 2001/83/EC is summarised in the table below.

	Active substances for human use	Active substance intermediates for human use	
Registration	Manufacturer	Yes	Yes
Distributor	Yes	No	
Importer	Yes	No	

1.1.30 EU GMP guide part IV: GMP requirements for advanced therapy medicinal products (ATMP): Guidelines on GMP specific to ATMPs

Questions and answers on the use of out-of-specification batches of authorised cell and tissue-based advanced therapy medicinal products

1. Under which circumstances can out-of-specification (OOS) batches of authorised cell/tissue based advanced therapy medicinal products (ATMPs) be administered?

In the exceptional circumstances set out in Section 11.5 of the Guidelines on GMP for ATMPs1, the administration of a cell/tissue-based ATMP that does not comply with the specifications set out in the marketing authorisation may be considered to avoid an immediate significant hazard to the patient. The supply of an OOS batch can only occur when the conditions laid down in Section 11.5 of the above-mentioned Guidelines are met, in particular that the manufacturer provides an evaluation of the risks to the treating physician and that the supply of the batch is requested by the treating physician after having considered the specific condition of the patient and the evaluation of the risks provided by the manufacturer. The manufacturer of the OOS batch should always be at the centre of the investigation of the root causes leading to the OOS result and of the evaluation of the risks. In cases where the manufacturer, importer and marketing authorisation holder (MAH) are different legal entities, there should be a written agreement between the parties which lays down the respective roles including also with regard to the communication with the treating physician and competent authorities.

2. Who should be notified and when?

When an OOS batch of a cell/tissue-based ATMP that has been granted a marketing authorisation is detected, the priority for the MAH/manufacturer/importer should be to immediately inform the treating physician and to conduct an evaluation of risks.

The competent authority that should be informed when a patient in the EU has been administered an OOS batch is the Supervisory Authority (Competent Authority responsible for granting the manufacturing authorisation to the site manufacturing or importing the medicinal product within the European Union).

Following the supply of the product at the request of the treating physician, it is expected that the manufacturer/importer/MAH informs the Supervisory Authority within 48 hours.

The manufacturer/importer/MAH should contact the National Authority of the treating site(s) to check if they have to be informed. Where required, the information should be provided to National Competent Authorities at the same time as the submission to the Supervisory Authority.

3. How should the manufacturer/importer/MAH notify the EMA of the OOS batch(es)?

In addition to informing the Supervisory Authority when a patient has been administered an OOS batch, the manufacturer/importer/MAH should provide a periodic review of the OOS batches that have been administered according to Section 11.5 of the Guidelines on GMP for ATMPs to the EMA (as the body responsible for the scientific evaluation and oversight of ATMPs that have been granted a marketing authorisation). This periodic review should be submitted by the MAH as a Quality Defect report2 every 6 months and should include an overview of the OOS batches compared to batches released according to specifications during the previous 6 months, with the objective of verifying the consistency of the existing process, the appropriateness of current specifications, to highlight any trends and to identify potential product and process improvements. EMA will provide this periodic review to the CAT Rapporteur of the authorised product. If a trend is detected, additional information might be requested and/or the need for regulatory actions will be considered.

4. Are there any other obligations or expectations that the manufacturer/importer and MAH have to follow in case of an OOS batch of a cell/tissue based ATMP that has been granted a marketing authorisation?

The obligations of the manufacturer/importer are not waived. Although it is acknowledged that the QP cannot certify the OOS batch, he/she has to ensure that the verifications on the batch have been performed. It follows that the import into the EU of OOS batches should follow standard import procedures. Additionally, the manufacturing/importing site should - as a minimum - keep records of all details concerning the manufacture, testing, transport and storage of the product, the request of the treating physician and the analysis of the risks provided by the MAH / manufacturer. The records on the investigation of the OOS result(s) and associated risk assessment in relation to the potential impact on product quality should also be available. The obligations of the MAH are also not waived. Therefore, pharmacovigilance reporting obligations or specific additional obligations to follow-up patients treated with the ATMP (e.g. registry) continue to apply in respect of OOS batches. 5. What information should be provided to the patient? The patient should be informed about the OOS ATMP the patient is going to receive. The information that shall be provided to the patient is governed by national legislation of the treating site. The information to patients should be provided in lay language. It is stressed that document(s) designed to inform patients can neither transfer any responsibilities to the patient nor discharge the responsibilities of the MAH or the manufacturer.

Questions and answers on the exemption from batch controls carried out on ATMPs imported into the European Union from a third country

1. What are the obligations of the Qualified Person (QP) regarding testing of batches for ATMPs imported into EU?

In the case of an authorised ATMP imported from a third country, the QP has to ensure that each batch has been manufactured in accordance with Good Manuafacturing Practice and that the quality is in accordance with the terms of the marketing authorisation. Imported ATMP batches have to be re tested upon importation into the EU, as required by Article 51(1)(b) of Directive 2001/83/EC. Article 51(2) of Directive 2001/83/EC, makes provision for the Qualified Person certifying the imported batch to rely on controls conducted in a third country (batch release testing in accordance with the terms of the marketing authorisation) where the product has been manufactured and tested in a country having a relevant mutual recognition agreement (or equivalent arrangements) (MRA) with the EU. The possibility to rely on controls conducted outside of the EU (where no relevant MRA on GMP is in place) is exceptional and cannot be applied beyond the specific scenarios described in the GMP Guideline for ATMPs.

2. In which cases can the exemption from EU batch re testing for imported ATMPs be granted?

The exemption from re-testing batches upon import into the EU for ATMPs may only be granted where the conditions laid down in paragraph 11.17 of the EU GMP guideline for ATMPs1 are met, specifically:
1) limited amount of material available;
Or
2) short shelf-life; 1Eudralex Volume 4 Good manufacturing practice "Guideline on Good manufacturing practice specific to Advanced Therapy Medicinal Products", at paragraph 11.17.
And
3) the testing in the third country should be conducted in GMP-certified facilities.

This exceptional exemption is primarily foreseen for imported patient-specific ATMPs (e.g. autologous product).
Technical difficulties in the transfer of analytical methods from third countries to the EU cannot be used as a basis to accept an exemption from re-testing of batches imported into the EU.
Requests for an exemption from batch re-testing in the EU for an imported ATMP should be supported by a justification and, where applicable, scientific data to substantiate the claim made (please refer to Question 3 below). The request and corresponding justification will be assessed by the CAT/CHMP during the evaluation of the marketing authorisation procedure.
As the EU GMP guideline for ATMPs requires that "in such cases, the testing in the third country should be conducted in GMP-certified facilities (in the case of authorised ATMPs)", a GMP pre-approval inspection is expected to be triggered unless a valid GMP certificate is available from an inspection carried out by an EEA competent authority, on the same or similar category of testing.
Applicants intending to rely on paragraph 11.17 of the GMP for ATMPs Guidelines to request an exemption from re-testing of batches imported into the EU are strongly advised to proactively consult with EMA early in product development.

3. Which data should be submitted in the marketing authorisation application to the EMA in order to justify the exemption from batch re-testing in the EU of imported ATMPs?

To substantiate the request, the applicant/MAH should provide at least the following data in the initial marketing authorisation application: • total batch size and number of units required for batch release testing;
• available stability data and proposed shelf life;
• analytical sampling plan;
• a GMP certificate issued by an EEA Competent Authority relevant to the particular category of testing at the facility located in the third country.

Changes to the particulars of the marketing authorisation, for instance upscaling of batch size, may annul the exemption granted if the ATMP no longer meets the criteria set out in the EU GMP guideline for ATMPs. In such cases, batch release testing would be required to be conducted in the EU, in accordance with Article 51(1)(b) of Directive 2001/83/EC. Questions and answers on the exemption from batch controls carried out on ATMPs imported into the European Union from a third country EMA/354272/2019 Page 2/3

4. What are the obligations of the Qualified Person for the batch release of imported batches exempted from re-testing in the EU?

The general obligations of the QP as laid down into the Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products2 are not waived for imported ATMPs subject to exemption from re-testing in the EU as regards to the requirements for performing the batch release. However, only in case of a granted exemption, the EU QP certifying the imported batch may rely on quality control testing in accordance with the terms of the marketing authorisation performed in a third country. The EU QP should have access to additional manufacturer documents (e.g. raw analytical data), as needed, in order to certify the imported batches.

Questions and answers on the principles of GMP for the manufacturing of starting materials of biological origin used to transfer genetic material for the manufacturing of ATMPs

1. How are starting materials for ATMPs defined?

ATMP starting materials are defined as all the materials from which the active substance is manufactured or extracted (see Part I of the Annex I to Directive 2001/83/EC on the Community code relating to medicinal products for human use, paragraph 3.2.1.1 b). In the case of genetically modified cells, the starting materials shall be the components used to obtain the genetically modified cells, i.e. the starting materials to produce the vector, the vector and the human or animal cells (see Part IV of the Annex I to Directive 2001/83/EC on the Community code relating to medicinal products for human use paragraph 3.2.1.5). Donation, procurement and testing of tissues/cells used as starting material are not concerned by principles of GMP but are governed by Directive 2004/23 or 2002/98/EC. When the tissues/cells used are outside the scope of the Directive 2004/23/EC or- as appropriate- Directive 2002/98/EC (e.g. cell-lines/cell banks established outside the EU, or cells procured before the entry into force thereof) section 7.3 of Part IV of the GMP Guide is applicable.

2. What does principles of GMP mean?

GMP requirements for ATMP active substances (drug substances) and ATMP finished products are described in Part IV of the GMP Guide. Some requirements of part IV can also be relevant for the starting materials. However, the main differences with regard to the starting materials are:

- Not all GMP aspects described in Part IV of the GMP Guide are required.
- According to the current legal framework, neither recurring inspections nor GMP certifications by the responsible authorities are required.

As a result of this situation, the ATMP manufacturers have the responsibility to verify that appropriate GMP requirements are implemented for the manufacturing/testing of the starting materials according to the methodology described in the questions 4 and 5 of the document.

3. When does principles of GMP apply to starting materials used for the manufacturing of ATMPs?

A manufacturing process for an ATMP can be designed in different ways. Consideration should be given to define which manufacturing process steps and quality control testing are applicable to ATMP starting materials, ATMP active substance, or ATMP finished product.

The table below gives examples of where GMP or GMP principles apply in the manufacturing process for ATMPs.

Example Products	Application of GMP to manufacturing steps is shown in dark grey GMP Principles should be applied where shown in light grey starting material - active substance - finished product →				
In vivo gene therapy: mRNA	Plasmid, manufacturing and linearization	In vitro transcription		**mRNA** manufacturing and purification	Formulation, filling
In vivo gene therapy: non-viral vector (e.g. naked DNA)	Plasmid manufacturing	Establishment of bacterial bank (MCB, WCB)		**DNA** Manufacturing fermentation and purification	Formulation, filling
In vivo gene therapy: viral vectors	Plasmid manufacturing	Establishment of a cell bank (MCB, WCB) and virus seeds when applicable		**Vector** Manufacturing and purification	Formulation, filling
Ex-vivo: genetically modified cells[3]	Donation, procurement and testing of tissues / cells[1]	Establishment of a cell bank (MCB, WCB) for plasmid and/or vector expansion and viral seeds when applicable	Plasmid manufacturing, Vector manufacturing	**Genetically modified cells** manufacturing	Formulation, filling

In the table above, the AMTP starting materials are underlined and the ATMP active substances appear in bold. The construction of the plasmid by in silico and molecular biological methods occurs before the plasmid manufacturing and is considered research and development. Therefore it is not under the scope of the current Q&A.

The following are non-exhaustive examples in the application of GMP to the manufacture of ATMP.

Figure 1: Example of gene therapy mRNA ATMP manufacturing

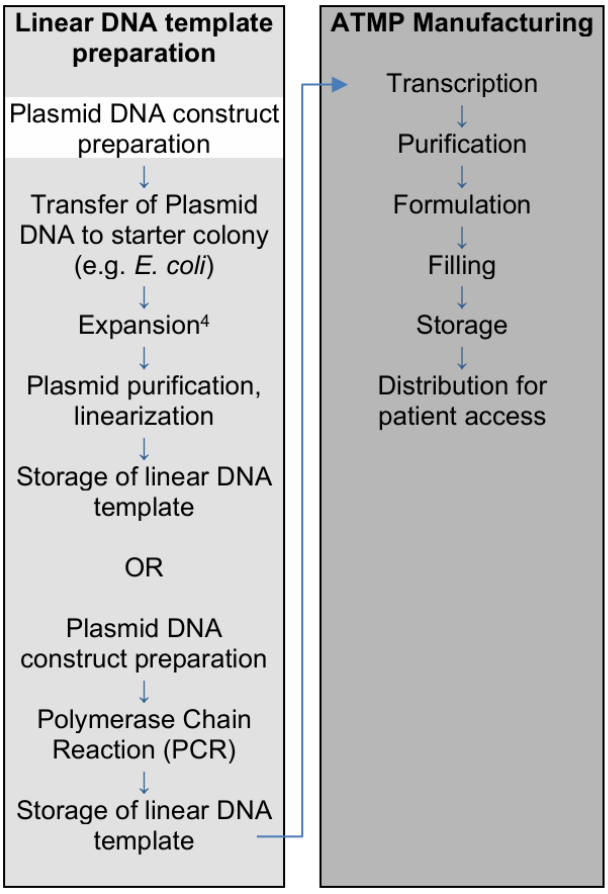
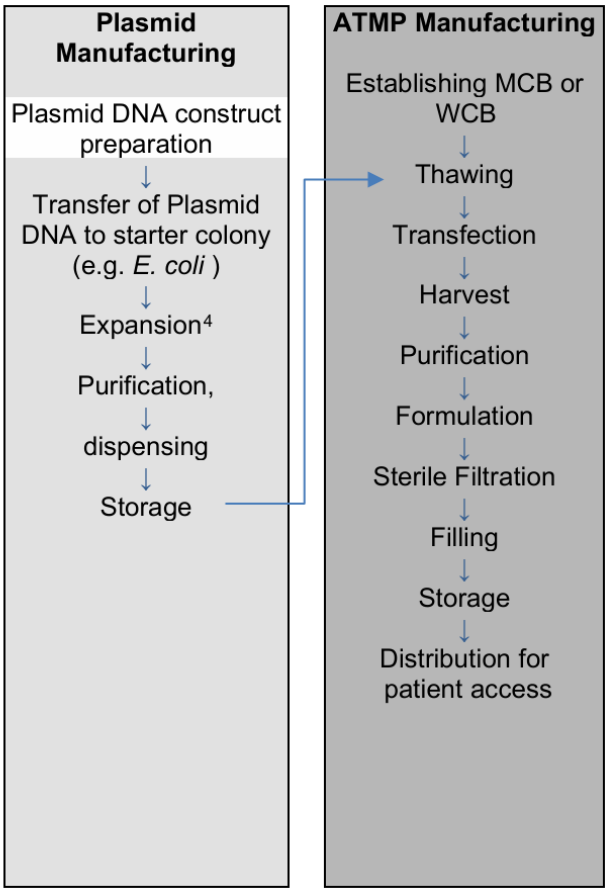


Figure 2: Example of in vivo viral vector gene therapy ATMP manufacturing



1.1.31 Requirements for active substances used as starting materials in veterinary medicinal products

1. Do active substances used as starting materials in veterinary medicinal products have to comply with Good Manufacturing Practices ("GMP") for active substances?

Yes, active substances used as starting materials in veterinary medicinal products imported or manufactured in the Union[1] have to be manufactured in accordance with GMP for active substances. This obligation, set out in Article 93(1)(j) of the Regulation applies regardless of whether the active substances are manufactured in the Union or in third countries. This obligation already existed under Directive 2001/82/EC. [2]

Until the specific GMP for veterinary medicinal products and active substances used as starting materials referred to in Article 93(2) of the Regulation (EU) 2019/6[3] (the Veterinary Medicines Regulation) are adopted, the Part II of the Good Manufacturing Practice Medicinal Products for Human and Veterinary Use on Basic Requirements for Active Substances used as Starting Materials, as well as relevant annexes, applies.[4]

[1] For the purposes of this document, reference to the Union should be understood as including also the EEA countries.
[2] Directive 2001/82/EC of the European Parliament and of the Council on the Community code relating to veterinary medicinal products (OJ L 311, 28.11.2001, p. 1).
[3] Regulation (EU) 2019/6 of the European Parliament and of the Council on veterinary medicinal products and repealing Directive 2001/82/EC, OJ L4, 7..01.2919, p.4.
[4] https://ec.europa.eu/health/medicinal-products/eudralex/eudralex-volume-4_en.

2. Are there new obligations for active substances used as starting materials in veterinary medicinal products under the Veterinary Medicines Regulation?

Yes, the Veterinary Medicines Regulation requires manufacturers and importers of veterinary medicinal products to:

- verify that manufacturers, importers and distributors within the Union from whom they source the active substances have registered their activities in the territory of the Member State where they are established;[1] and
- perform audits based on a risk-assessment on the manufacturers, distributors and importers from whom they source the active substances.[2]

Manufacturing sites of active substances established outside the Union territory are not required to register their activities in accordance with Article 95 of the Regulation. However, to the extent that the active substances are used in veterinary medicinal products marketed in the Union, the manufacturer or importer of the relevant veterinary medicinal products is required to audit these sites.

The existence of valid GMP certificate for a manufacturing site of active substance(s), issued by a Union authority or by the authority of a third country in the context of a valid mutual recognition agreement, can be taken into consideration by manufacturers and importers of veterinary medicinal products, together with other supporting information in a risk-based approach, to determine the extent of the auditing obligations of manufacturers of finished medicinal products foreseen in Article 93(1)(l) of the Regulation (*i.e.* to establish priorities for its own audit programme of suppliers of active substances).[3]

While manufacturing sites of active substances used as starting materials in veterinary medicinal products may, therefore, have an interest to obtain a GMP certificate from a Union competent authority, reference is made to question 5, in connection with the requests for voluntary inspections.

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[1] Article 93(1)(k) and Article 95 of the Veterinary Medicines Regulation.
[2] Article 93(1)(l). It is noted that the conduct of audits was already foreseen as part of the recommendations in the Good Manufacturing Guidelines (*e.g.* Section 5.29 of the Chapter 5, Part I of the EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use).
[3] Article 93(1)(l) and Article 95 of the Veterinary Medicines Regulation.
[4] Reference is also made to EMA Q&A on EU GMP guide part II: Basic requirements for active substances used as starting materials: GMP compliance for active substances, question n°2.

3. How is a GMP certificate issued?

Article 94(1) to (3) of the Veterinary Medicines Regulation describes the procedure to issue a GMP certificate, after a successful inspection has been conducted. If the outcome of the inspection is that the site does not comply with EU GMP, this information shall be entered into the manufacturing and wholesale distribution database.

Pursuant to Article 2(2) of the Regulation, the same procedure applies for certificates for manufacturing sites of veterinary medicinal products and for certificates for manufacturing sites of active substances used as starting materials, regardless whether they are established in the Union or outside.

For aspects relevant to requests of voluntary inspections, reference is made to question 5.

4. Is a GMP certificate mandatory for manufacturing sites?

Manufacturing sites of veterinary medicinal products must have an EU GMP certificate, regardless of whether they are located in the Union or outside. Specifically, Article 94(5) of the Veterinary Medicines Regulation requires that importers of veterinary medicinal products ensure that any manufacturing site of such products established outside the Union has a GMP certificate issued by Union competent authorities, unless a mutual recognition agreement between the Union and the third country applies.[1]

However, manufacturing sites that only produce active substances used as starting materials in veterinary medicinal products are not required to have a GMP certificate.[2] Compliance with EU GMP for active substances must however be ensured as explained in questions 1 and 2.

[1] Reference is also made to the Compilation of Union Procedures on Inspections and Exchange of Information:

[2] Article 2(2) provides that Articles 94 and 95 apply also to active substances used as starting materials. This cross-reference should be read in conjunction with the specific wording of the cross-referred provisions. To this effect, it is noted that Article 95 specifically deals with active substances used as starting materials, while paragraphs (1) to (4) of Article 94 are neutrally worded and apply therefore to both finished products and active substances. In contrast, paragraph (5) of Article 94 explicitly refers to veterinary medicinal products and not to active substances.

Furthermore, to consider that manufacturing sites of active substances established outside the Union should have a GMP certificate would contradict the general scheme of the Regulation, including the requirement for audits (new obligation for importers and manufacturers of veterinary medicinal products to guarantee that active substances have been manufactured in accordance with GMP) and would run against one of the main objectives of the legislation; namely, to increase the availability of veterinary medicinal products.

5. Can manufacturers of active substances used as starting materials in veterinary medicinal products apply for a GMP inspection on a voluntary basis?

Yes. The request for the inspection should be made to the EEA competent authority where the site is located or, in case of sites located in third countries, to a competent authority where the active substance used as starting material is used in the manufacture of veterinary medicinal products, or the Member State where the importer is established. If this is not the case, any EEA authority can be approached.

There is no guarantee that such a request will be fulfilled since competent authorities primarily use risk-based principles to plan inspections. Thus, when a manufacturer of active substance(s) used as starting material in veterinary medicinal products applies for a voluntary inspection, this does not constitute an obligation for the competent authority to trigger an inspection.

The procedure for issuing an EU GMP certificate under paragraphs (1) to (3) of Article 94 is applicable to manufacturers of active substances used as starting materials (*see* also question 3).

Finally, it is stressed that manufacturers/importers are required to ensure that only active substances manufactured in accordance with applicable GMPs are used.[1] An inspection of the active substance manufacturer by an EEA authority does not exempt a manufacturing authorisation holder from this responsibility but, as explained in question 2, may be relevant to determine the extent of the audits.

[1] Article 93(1)(j).

6. Can manufacturers of active substances used as starting materials in veterinary medicinal products imported or manufactured in the Union be inspected by a Union authority?

Yes. Article 94(4) of the Veterinary Medicines Regulation (in conjunction with Article 2(2) thereof) encompasses both manufacturing sites of finished veterinary medicinal products and manufacturing sites of active substances used in veterinary medicinal products. It follows that national competent authorities, the Agency, or the European Commission can request an inspection of a manufacturer of active substance used as a starting material, including third country manufacturers.

These inspections may be carried out:

1. As part of the registration of manufacturers of active substances established in the Union (Article 95);
2. In the scope of the regular risk based verifications to manufacturers/importers of veterinary medicinal products and manufacturers/importers of active substances. Article 123(1) of the Regulation requires competent authorities to carry out controls of both importers of manufacturers/importers of veterinary medicinal products and manufacturers/importers of active substances. Those controls should be carried out regularly, in accordance with a risk-based approach, taking into account at least:

- the intrinsic risks associated with the activities of the site and the location thereof;
- the past record as regards the results of controls performed on the sites and previous compliance;
- any information that might indicate non-compliance;

- the potential impact of non-compliance on public health, animal health, animal welfare and the environment.

3. In order to verify whether the data submitted for obtaining a certificate of suitability complies with the monographs of the European Pharmacopoeia when the starting material concerned is subject to a European Pharmacopoeia monograph (Article 125).
4. At the request of a third country competent authority in the context of a mutual recognition agreement ("MRA").

7. Can inspections conducted by third country competent authorities be considered when deciding whether a Union inspection should be triggered?

Yes, when there is a MRA is in place covering GMP for active substances, the outcome of inspections performed by the MRA partner authority will be taken into consideration when deciding whether an inspection of a manufacturing site of active substances used as starting materials is necessary.

1.2. Questions & answers on quality of herbal medicinal products/traditional herbal medicinal products

Testing

(1) *Question*

A mixed extract is produced by simultaneous extraction of several herbal substances with the same extraction solvent. Is it acceptable to perform an analysis using only one representative analytical marker for stability testing of the herbal medicinal product?

Answer

In principle mixed extracts should fulfil the same requirements as mixtures of single extracts and the individual extracts within the mixture should be quantified. Mixed extracts are produced in a special manufacturing process as a unique extract, but these extracts contain the specific extracts from the different individual herbal substances.
The analytical methods should be selected as prescribed in the *Guideline on quality of combination herbal medicinal products/traditional herbal medicinal products* (EMEA/HMPC/CHMP/CVMP/214869/2006).

(2) *Question*

'In practice it is sometimes difficult to find suitable analytical markers for quantitative purposes. Can primary metabolites of herbal substances also be used as analytical markers for stability testing in case suitable secondary metabolites are not available? Is this also possible for release testing?'

Answer

The EMA *Reflection paper on markers used for quantitative and qualitative analysis of herbal medicinal products and traditional herbal medicinal products* (EMEA/HMPC/253629/2007) gives an overview on possibilities and problems with markers. Markers (analytical markers) should ideally be characteristic or specific for the plant/herbal preparation and also stability-indicating at the same time. However, this may not always be fulfilled. Where a marker is unstable in normal conditions of use ("poor analytical tool"), it may not be suitable for determination of an appropriate shelf-life. In some cases, due to low concentrations present or where a chromophore is lacking, potential marker substances may not be readily detectable by the usual chromatographic methods. In many cases marker substances occur in groups of structurally related constituents and a selective separation is difficult (e.g., tannins, proanthocyanidins, saponins, etc.). It is generally assumed that markers should belong to the group of "secondary" plant metabolites such as flavonoids, saponins, terpenes, phenols etc. However, in exceptional cases markers from the group of primary metabolites such as carbohydrates, amino acids/proteins, fats, etc. may be acceptable, if they allow the specific determination of the content of a herbal preparation within a herbal medicinal product (e.g., carbohydrates in linseed, fatty acids in saw palmetto). Such an approach is applicable to both release testing and stability testing.

(3) *Question*

'Is testing of benzene (class 1 solvent) for herbal preparations necessary?'

Answer

Some solvents used for extraction, purification or during manufacture of a herbal preparation may contain benzene as an impurity. As a consequence, the potential for benzene residues occurring inherbal preparations and solvents used in their production should be addressed and appropriate controls applied, unless otherwise justified.[2]
Benzene may be an impurity in solvents such as: acetone, ethanol, methanol, isopropanol, toluene, xylene, hexane, cyclohexane and petroleum ether.
The most commonly used solvents for the manufacture of herbal preparations are ethanol and water or combinations thereof. Ethanol of chemical origin may contain benzene as an impurity whereas ethanol obtained from fermentation does not normally contain any benzene. Therefore the production process

of ethanol used in herbal preparations should be taken into account when considering the need for tests in the specification to control the benzene content and the frequency of testing.
Ethanol, methanol and acetone complying with their European Pharmacopoeia monographs should not exceed 2 ppm of benzene, which is the ICH limit. The content of benzene in solvents used in the manufacture of herbal preparations, which are not covered by monographs in the European Pharmacopoeia, should, preferably, not exceed the ICH limit (2 ppm). Where solvents exceeding the ICH limit are used, potential benzene residues should be identified and quantified.
Where the herbal preparation is a liquid extract or tincture prepared by simple methods without concentration steps using ethanol/water mixtures in accordance with the European Pharmacopoeia, potential benzene residues will not exceed the ICH limit applied to the starting extraction solvents. In such cases, further controls on potential benzene residues are not required.
Where the herbal preparation is a liquid extract or tincture prepared by processes involving more complex processes and concentration steps the potential for benzene residues to exceed the ICH limit of 2 ppm in the resulting preparation needs to be addressed and appropriate controls applied if needed.
Where the herbal preparation is a semi-solid preparation (soft extracts and oleoresins), the extraction solvent(s) and/or other solvents used during purification and manufacture may only be partially removed in the case of some semi-solid preparations. In these cases the potential for benzene residues should be addressed and appropriate controls applied if needed. The limit should not exceed 2 ppm.
Where the herbal preparation is a dry extract, the benzene content would be expected to be reduced during the drying process. However, the relative volatility of all solvents used in manufacturing process and of benzene (bp 80.1°C) must be taken into account.
In the case of dry extracts benzene levels should be addressed and appropriate controls applied if needed. The limit should not exceed 2 ppm.

[2] See Annexes to: CPMP/ICH/283/95 Impurities: Guideline for residual solvents (CPMP/QWP/450/03, Rev.1): Annex I: B class 1 solvents present as an impurity.

Contaminants

Mycotoxins

(1) *Question*

'With regard to the determination of mycotoxins, when is routine testing required and in what circumstances would reduced testing or possibly no testing be acceptable?' *Rev. Nov. 2023*

Answer

In general testing for mycotoxins should be carried out for herbal substances. However, routine testing for mycotoxins is not required for all herbal substances, because only a few herbal substances are at risk of contamination. An appropriate risk assessment should be undertaken, taking account of the plant and the plant part. Routine analysis of mycotoxins should be considered in the case of a herbal substance/plant part at risk such as seed, fruit, root, rhizome. If, in the literature, data are available on mycotoxin formation in the plants, or possible contamination of the herbal substance is known, then testing should be conducted. In addition, as aflatoxins and ochratoxin A are soluble in alcohol, the need for testing of the herbal preparation should also be considered.
For plant/plant parts, not at a particular risk, monitoring would suffice in general and reduced testing (or even omission of testing) may be acceptable if justified. Appropriate harvest/collection, drying and storage procedures reduce the risk for contamination with mycotoxins. For example, drying of the material following harvest as quickly as possible with a homogeneous loss on drying of < 12% (or even < 10%) as control measure reduces the risk. A reduced water activity (Aw) will assist in the prevention of contamination. The water activity requirements for the growth of different Gram-reactive bacteria, bacterial spores, yeasts and moulds are described in the literature[3, 4]. It is generally recognised that in products with water activity below 0.60, moulds and yeasts do not proliferate.

[3] Troller et al. Measurement of water activity. In: Compendium of methods for the microbiological examination

of foods. American Public Health Association, Washington DC, 1984, pp. 124-134.

[4] USP, chapter <1112> Microbiological attributes of non sterile pharmaceutical products - Application of water activity determination. US Pharmacopoeia Convention, Inc. 31th edition, 2007.

Microbiological quality

(1) *Question*

'Is it possible to use skip testing for the microbiological quality of herbal medicinal products in specifications for stability studies performed under accelerated/intermediate conditions?' *Rev. Nov. 2023*

Answer

No. The optimal growth temperature of some microorganisms, especially human-pathogenic microorganisms, is in the range of 30°C to 40°C. Particularly in combination with a high relative humidity (e.g., 75 %) these are optimal growth conditions for some microorganisms (see the *Reflection paper on microbiological aspects of herbal medicinal products and traditional herbal medicinal products* (EMA/HMPC/95714/2013). Therefore, the testing of the microbiological quality is essential for these studies, as a minimum requirement compliance should be demonstrated at the beginning (batch release) and at the end of stability studies.

(2) *Question*

'Is it possible to replace the testing of the microbiological quality by the testing of the water activity (AW)?'

Answer

Products, brought to market in the EU, must follow the requirements of the European Pharmacopoeia. Therefore, at least at the beginning (batch release) and at the end of a stability study the conformity to the European Pharmacopoeia must be demonstrated. The testing of water activity can give additional information during the stability study, but it cannot replace a necessary microbiological testing.

Elemental impurities

(1) *Question*

(Traditional) herbal medicinal products are out of the scope of ICH guideline Q3D on elemental impurities. Additionally, the reference to the Ph. Eur. 2.4.8 heavy metals test has been deleted from Ph. Eur. individual monographs. How should (traditional) herbal medicinal products be evaluated with respect to content of elemental impurities? *Rev. Nov. 2023*

Answer

Guideline ICH Q3D on elemental impurities for human medicinal products came into effect in June 2016 for new products and in December 2017 for already authorised products. According to ICH Q3D, control of elemental impurities should be performed by the marketing authorisation holder/registration holder, by an overall risk assessment of the entire product. In general, active substances, excipients, water, packaging materials and equipment should be taken into consideration.
ICH Q3D was implemented in Ph. Eur. 9.3 by the general monograph *Pharmaceutical preparations* and Ph. Eur. 5.20 *Elemental impurities*. The test for heavy metals, Ph. Eur. 2.4.8, was deleted from individual monographs for human use by Ph. Eur. 9.0.
(Traditional) herbal medicinal products are out of the scope of ICH Q3D and Ph. Eur. 5.20, as different provisions on herbal products apply in the various ICH regions, while in the EU, the quality of (traditional) herbal medicinal product should be ensured at the same level as for other medicinal products.
Herbal substances should comply with the limits for heavy metals specified in the Ph. Eur. monograph on herbal drugs (1433). A risk assessment is in general requested by GMP guidelines. However, it is

also the marketing authorisation/registration holders' responsibility that the *principles* of risk assessment are applied for controlling the levels of elemental impurities in the products.
This should be fulfilled for (traditional) herbal medicinal products for human use. For herbal medicinal products for veterinary use, further scientific guidance will be elaborated by the EMA.
For new applications, a *summary* of the risk assessment covering the risk evaluation for elemental impurities should be included in the application.
For already authorised/registered products, variation applications should only be submitted in cases where the risk assessment triggers changes in the quality of the product (e.g., change in impurity tests).

Manufacturing

(1) *Question*

'Is it acceptable to mix batches of 'other' extracts in order to improve the batch-to-batch consistency?' *New Nov. 2023*

Answer

Yes, it is acceptable to mix batches which are compliant with the release specification. However, it is not acceptable to use as criterion the content of an analytical marker alone, as this would resemble the manufacture of a quantified extract. Also, chromatographic fingerprints have to be used to justify mixing and to demonstrate the benefit of such a step with regards to the extract in its entirety. Moreover, the natural variability should be considered. It is not acceptable at all to mix batches which do not comply with the release specification in order to achieve a compliant pooled batch.

Quality of water

(1) *Question*

'For the manufacture of herbal extracts, water complying with the Ph. Eur. monograph 2249 (water for preparation of extracts) may be used. In the case of liquid extracts, this water would be part of the herbal medicinal product. In contrast, Ph. Eur. requires for the preparation of medicines the use of purified water. Is it therefore required to use for the manufacture of liquid extracts purified water?' *New Nov. 2023*

Answer

No. The extraction solvent is integral part of the herbal substance and not considered as an excipient. Therefore, it is acceptable to use *water for preparation of extracts* (Ph. Eur. monograph 2249) in the manufacture of liquid extracts, which are used as such in herbal medicinal products.

Stability

(1) *Question*

'A medicinal product is manufactured by an interrelated production process comprising the production of the active substance and the production of the finished product. Example: The active substance is a powdered herbal substance in hard capsules. The maximum time frame between powdering and production of the finished medicinal product is three months. Are stability studies necessary for both the active substance and the finished product?' *Rev. Nov. 2023*

Answer

In the case of an interrelated production process such as that described above, the stability testing has only to be performed on the herbal medicinal product. However, justification is needed for the choice of the packaging material, transportation and storage conditions for the active substance.

(2) *Question*

'A herbal tea consists of a mixture of cut herbal substances packaged in a multi-dose bag. Are comprehensive stability studies necessary for both the active substances and the finished product?'

Answer

Provided that comparable packaging material is used, the stability tests on the active substances are not necessary if each of the active substances can be determined by an appropriate assay method in the finished product throughout the shelf life.
Alternatively, in special cases, where stability data for each active substance in the finished dosage form exist and interactions between the active substances are unlikely, the stability tests for the finished product can be replaced by the stability data for the single active substances.

(3) *Question*

'Is it possible to make reference to stability data obtained from comparable herbal preparations (from the same herbal substance) when both active substances are covered by the same Ph. Eur. monograph?'

Answer

As most Ph. Eur. monographs for herbal preparations cover different extraction solvents and DERs and, in addition, the excipients and packaging materials are not part of the monograph, it is necessary to establish stability data for each individual active substance. In very exceptional cases, it may be possible to make reference to a closely related preparation provided satisfactory justification is given.

(4) *Question*

'Where it is evident from former stability studies on laboratory/pilot batches that the finished product is unstable under accelerated and/or intermediate conditions are further studies still required under such conditions?' *Rev. Nov. 2023*

Answer

In the case of herbal medicinal products, in situations where former stability studies are available, demonstrating that the finished product is unstable under accelerated and/or intermediate conditions, it may be acceptable in such cases to justify the omission of further stability studies under accelerated/intermediate conditions.

(5) *Question*

'Are stability overages for herbal active substances acceptable?'

Answer

In general, as the whole herbal substance/preparation is considered as the active substance, stability overages would not be acceptable. However, stability overages would be acceptable for standardised extracts if justified.

Essential oils as active substances

(1) *Question*

Many essential oils are produced by farmers or small manufacturers. In some countries essential oils are not classified as "active pharmaceutical substances" and in other countries it is difficult to control the GMP status during the first production step. Is it acceptable that the production process is in line with local regulations and not with GACP principles and EU GMP?

Answer

No, it is stated in Directive 2011/62/EU and in detail for herbal medicinal products in the GMP Guideline, Annex 7, that all active substances should be produced in line with EU regulations.

However, early production steps could follow the GACP principles if the last steps were in line with GMP. Similar standards can be accepted if justified (including risk assessment). Where the active substance is produced in non-EU countries, compliance with written confirmation according to the provisions of the Directive 2011/62/EU is required.

(2) *Question*

Is it permissible to blend essential oil sub-batches which are not in line with the chromatographic profile of the relevant Ph. Eur. monograph?

Answer

Sub-batches may be blended or further processed to be brought in line with the chromatographic profile of the relevant Ph. Eur. monograph. In some cases the Pharmacopoeial limits are based on blended and/or processed essential oils, therefore it is sometimes necessary to extend the limits for primary batches. In these cases; appropriate fixed limits should be justified on the basis of sufficient batch data and the plant material used for distillation should be adequately controlled. These limits should be approved by the competent authority.

1.3 Questions and answers (version 22) - Safety features for medicinal products for human use

1. General

1.1. Question: What are the safety features?

Answer: The safety features consist of two elements placed on the packaging of a medicinal product:

(1) a unique identifier, a unique sequence carried by a two-dimensional barcode allowing the identification and authentication of the individual pack on which it is placed; and

(2) a device allowing the verification of whether the packaging of the medicinal product has been tampered with (anti-tampering device).

1.2. Question: When do the rules on the safety features apply?

Answer: They apply as of 9 February 2019. Belgium, Greece and Italy have the option of deferring the application of the rules by an additional period of up to 6 years.

Belgium has however formally renounced using this option and confirmed the application of the new rules as of 9 February 2019.

1.3. Question: Do the safety features need to be applied on all medicinal products for human use?

Answer: No. The safety features should only be applied on the packaging of the following medicinal products for human use:

(1) medicinal products subject to prescription which are not included in the list set out in Annex I to of Commission Delegated Regulation (EU) 2016/161;

(2) medicinal products not subject to prescription included in the list set out in Annex II of Commission Delegated Regulation (EU) 2016/161.

(3) medicinal products to which Member States have extended the scope of the unique identifier or the anti-tampering device to in accordance with Article 54a(5) of Directive 2001/83/EC.

1.4. Question: Are there exceptions from the requirements for certain medicinal products to bear or not the safety features?

Answer: Yes. The list of categories of medicinal products subject to prescription which shall not bear the safety features are set out in Annex I of Commission Delegated Regulation (EU) 2016/161, while the list of medicinal products not subject to prescription which shall bear the safety features are set out in Annex II of the same Regulation.

1.5. Question: Do the rules on the safety features also apply to veterinary medicinal products?

Answer: No. The rules apply only to medicinal products for human use. 4

1.6. Question: Do the rules on the safety features apply to medicinal products intended for research and development trials?

Answer: Medicinal products intended for research and development trials and not yet granted a marketing authorisation are excluded from the rules on the safety features.

Authorised medicinal products have to fulfil the requirements of Directive 2001/83/EC and Commission Delegated Regulation (EU) 2016/161 up to the moment it becomes known which batch/unit will be used for research and development trials. In practice, there are two possible situations:

1. The product is manufactured for known use in a clinical trial

An investigational medicinal product (IMP) that is manufactured in accordance with the marketing authorisation but is packaged for a clinical trial (not in the commercial presentation) is excluded from the rules on the safety features as it is solely manufactured and packed for the use in the clinical trial. The manufacturer would be required to hold a manufacturing and importation authorisation covering IMPs and the IMP certified under that authorisation in accordance with the clinical trial application noting that the clinical trial application must reflect these arrangements.

Authorised auxiliary medicinal products cannot be manufactured under a manufacturing and importation authorisation covering IMPs and must fulfil the requirements of a marketed pack bearing safety features and decommissioned appropriately (see below).

2. The product is authorised and sourced from the regulated supply chain

Medicines in their commercial presentations bearing safety features should be decommissioned in accordance with Articles 16 and 25(4)(c) of Commission Delegated Regulation (EU) 2016/161 before use as investigational medicinal products or authorised auxiliary medicinal products.

1.7. Question: Are the safety features required where the medicinal product manufactured in the EU is destined for exportation only?

Answer: No.

1.8. Question: In the case of a medicinal product bearing the safety features is brought into the territory of a Member State in accordance with Article 5(1) of Directive 2001/83/EC, do the rules on the safety features apply?

Answer: When a medicinal product is brought into the territory of a Member State in accordance with Article 5(1) of Directive 2001/83/EC, the rules on the safety features in principle do not apply, unless there is applicable national legislation requiring otherwise.

Member States can, however, use national legislation to regulate which provisions of Directive 2001/83/EC or of Commission Delegated Regulation (EU) 2016/161 apply to Article 5(1) products brought into their territory. Member States can, for example, require the mandatory verification/decommissioning of Article 5(1) products in accordance with Commission Delegated Regulation (EU) 2016/161.

In the absence of national legislation requiring otherwise, the rules on the safety features do not apply. The "importer" of a medicinal product brought into the territory of a Member State in accordance with Article 5(1) is not required, for example, to (re)place the safety features on its packaging (e.g. through labelling/relabelling operations) or to upload the unique identifiers, if present, into the national repository of the new Member State of destination. The verification of the safety features and decommissioning of the unique identifiers of Article 5(1) products already bearing the safety features are also not mandatory.

Pharmacies, healthcare institutions and other relevant stakeholders in that Member State are nevertheless strongly encouraged to verify the authenticity of and decommission the medicinal product before supplying it to the public.

1.9. Question: Does an obligation to bear "the safety features" imply an obligation to bear both a unique identifier and an anti-tampering device?

Answer: Yes.

1.10. Question: Once Commission Delegated Regulation (EU) 2016/161 applies, can manufacturers place the safety features, on a voluntary basis, on medicinal products not required to bear the safety features?

Answer: No. Once Commission Delegated Regulation (EU) 2016/161 applies, manufacturers cannot place the safety features on medicinal products not required to bear the safety features, unless the Member States have extended the scope of application of the unique identifier or of the anti-tampering device to those medicinal products in accordance with Article 54a(5) of Directive 2001/83/EC.

1.11. Question: Are medicinal products allowed to bear the anti-tampering device, if they are not required to bear the safety features?

Answer: Under Commission Delegated Regulation (EU) 2016/161,", medicinal products can only bear an anti-tampering device if they are in the scope of Article 54a(1) of Directive 2001/83/EC (i.e. if they are medicinal products subject to prescription or medicinal products listed in Annex II of Commission Delegated Regulation (EU) 2016/161) or if the Member State(s) where they are placed on the market extended the scope of the anti-tampering device to those medicinal products.

1.12. Deleted

1.13. Question: Will the mandatory changes to the packaging due to the placing of the unique identifier and of the anti-tampering device require the submission of variations to marketing authorisations?

Answer: The regulatory requirements to be followed to notify the EMA of the placing of the unique identifier and/or the anti-tampering device on centrally authorised products are detailed in an implementation plan developed by the EMA and the European Commission and published in the "product information templates" section of the EMA website: https://www.ema.europa.eu/en/documents/other/implementation-plan-introductionsafety-features-packaging-centrally-authorised-medicinal-products-human-use_en.pdf.

The regulatory requirements for nationally authorised products are available on the HMA/CMDh website: https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Falsified_Medicines /CMDh_345_2016_Rev00_02_2016_1.pdf.

1.14. Question: Are there any mandatory specifications for the anti-tampering device?

Answer: In accordance with Article 54(o) of Directive 2001/83/EC and Article 3(2)(b) of Commission Delegated Regulation (EU) 2016/161, an anti-tampering device has to allow the verification of whether the packaging of the medicinal product has been tampered with.

The integrity of the antitampering device should indicate whether the packaging has been opened or altered since it left the manufacturer, thereby ensuring that the content of the packaging is authentic. It should be possible to demonstrate that if the ATD is removed or broken, this is evident visually from the pack. The tamper evident nature should also be proven throughout the shelf life of the medicinal product.

In particular, the ATD should not break under normal conditions of handling in the supply chain without using e.g. source of heat or external tool. The quantity and quality of the materials used for the ATD and the packaging should be appropriate to ensure the effectiveness of the anti-tampering feature.

1.15. Question: Will the pharmaceutical companies receive any financial support (EU or national) for acquiring the instrumentation for applying the safety features on individual packages?

Answer: No, it is not currently foreseen that pharmaceutical companies will receive any financial support (EU or national) for acquiring the instrumentation for applying the safety features on individual packages.

1.16. Question: Who shall bear the financial responsibility for the covering the expenses of establishment and implementation of the repository system?

Answer: In accordance with Article 31(1) of Commission Delegated Regulation (EU) 2016/161, the repositories system shall be set up and managed by a non-profit legal entity or non-profit legal entities in the Union by manufacturers and marketing authorisation holders. The costs of the system shall be borne by the manufacturers of medicinal products bearing the safety features in accordance with Article 54a(2)(e) of Directive 2001/83/EC.

1.17. Question: Are radiopharmaceuticals required to bear the safety features?

Answer: No. All pharmaceutical forms and strengths of radiopharmaceuticals (as defined by Article 1(6) of Directive 2001/83/EC), radionuclide generators (as defined by Article 1(7) of Directive 2001/83/EC), radionuclide precursors (as defined by Article 1(9) of Directive 2001/83/EC) and kits (as defined by Article 1(8) of Directive 2001/83/EC) shall not bear safety features.

The wording of Article 54(o) of Directive 2001/83/EC ("medicinal products other than radiopharmaceuticals") excludes radiopharmaceuticals, as defined by Article 1.6 of the said Directive, from the scope of the safety features. Consequently, any medicinal product fulfilling the definition of radiopharmaceutical shall not bear the safety feature. Since radiopharmaceuticals are outside of the scope of the safety features, their addition to Annex I of Commission Delegated Regulation (EU) 2016/161 is unnecessary.

1.18. Question: Concerning pandemic-influenza vaccines, the EMA mock-up procedure allows a vaccine to be developed and authorized in advance of a pandemic, containing a strain of flu virus that few people have been exposed to but that could potentially cause a pandemic. These can be modified into pandemic-influenza vaccines in a future pandemic case. After a pandemic has been declared there is an emergency procedure for the final vaccine. Are there exceptions from the requirements for pandemic-influenza vaccines to bear or not the safety features?

Answer: No, as pandemic influenza vaccines are not included in Annex I of Commission Delegated Regulation (EU) 2016/161. Pandemic–influenza vaccines authorised via the mock-up procedure should bear the safety features in accordance with the said Regulation.

1.19. Question: In case of a bundle of several single packs sold as one unit, should the anti-tampering device and unique identifier be placed on the bundle packaging or on each single pack?

Answer: Whether a manufacturer needs to place the safety features on the bundle packaging or on each single pack within the bundle depends on how the medicinal product is described in its marketing authorisation dossier – regardless of what is the commercial sellable unit.

If, in the marketing authorisation dossier, the product presentation is described as a "multi-pack", the outer packaging as that of the bundle and the single packs as not for individual sale (the text 'can't be sold separately' or equivalent is present on the packs), then both the UI and the ATD need to be placed on the bundle packaging. The outer packaging must include, in addition to the unique identifier and ATD, all applicable labelling requirements as laid down in Article 54 of Directive 2001/83/EC.

If, however, the marketing authorisation dossier of the medicinal product describes the product presentation as a single pack and the text 'can't be sold separately' or equivalent is not present on the packs, then each pack within the bundle needs to be serialised and have an anti-tampering device. In this case, the bundle packaging should not bear a unique identifier, but it may bear an aggregated code containing the information on all unique identifiers within the bundle.

1.20. Question: If a pack bearing the safety features is lawfully opened (e.g. by parallel traders/manufacturers replacing the leaflet under the supervision of national competent authorities), can it be resealed (e.g. by applying a new ATD on top of the old, broken ATD)?

Answer: Yes, such package can be resealed (e.g. by applying a new ATD on top of the original, broken ATD) provided the requirements in Article 47a (1) of Directive 2001/83/EC are fulfilled.

This implies that:

(a) the authenticity of the unique identifier and the integrity of the ATD on the original pack were verified as authentic before breaking the original ATD/pack.

(b) the replacement of the ATD is conducted in accordance with applicable Good Manufacturing Practice principles and is subject to supervision by the competent authority.

c) the replacement ATD must make it possible to verify, with the same effectiveness as an original ATD, that the outer packaging of a medicinal product has not been unlawfully opened - tampered with - between the time at which that medicinal product is repackaged and that at which it is supplied to the public. This assumes that it is evident for everybody that a new ATD has been placed and by whom. The latter implies that the repackager of the medicinal product must be clearly stated on the outer packaging.

1.21. Question: Is it possible for manufacturers/wholesales/parallel traders to market/supply medicinal products with a packaging showing visible signs of opening/intrusion, but where the ATD has been replaced by a new ATD in accordance with Article 47a of Directive 2001/83/EC?

Answer: Yes, this is possible if the presence of visible signs of opening on the packaging are consistent with legal repackaging of that medicinal product by a parallel importer or by a parallel distributor.

It should be noted that Articles 24 and 30 of Commission Delegated Regulation (EU) 2016/161 prohibit wholesalers and persons authorised or entitled to supply medicinal products to the public who receive a medicinal product having a packaging showing signs of tampering from supplying that product. So they must be free of doubt that traces of opening are attributable to the repackaging of that medicinal product by an authorised parallel importer or by a parallel distributor.

1.22. Question: In case of parallel-traded packs, can parallel traders cover or remove the safety features of the original pack?

Answer: Parallel traders covering or removing the existing safety features are required to place equivalent safety features in accordance with Article 47a of Directive 2001/83/EC (see also Q&A 1.20).

The new unique identifier should comply with the requirements of the Member State where the medicine is intended to be placed on the market (Article 17 of Commission Delegated Regulation (EU) 2016/161).

Furthermore, if the product code and/or batch number of the parallel-traded product change compared to the original product, parallel traders must place a new unique identifier after first decommissioning the original one. For further details on the requirements for batch numbers appearing on the packaging of medicinal products subject to parallel trade, see Q&A 4 under 'EU GMP guide part I: Basic requirements for medicinal products: Chapter 5: Production' on the EMA website.[3]

When placing an equivalent unique identifier, parallel traders are required to fulfil, inter alia, the obligations laid down in Articles 33, 40 and 42 of Commission Delegated Regulation (EU) 2016/161 concerning the uploading and keeping up to date of the information on the new unique identifier into the repositories system.

In all cases, traceability must be maintained in the repository system in accordance with Article 35(4).

[3] https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing practice/guidance-good-manufacturing-practice-good-distribution-practice-questions-answers#eugmp-guide-part-i:-basic-requirements-for-medicinal-products:-chapter-5:-production-section

1.23. Question: Is it possible to place a transparent sticker used as an ATD over the human readable codes or the 2D Data Matrix, even if opening the pack might lead to the human-readable data and/or 2D barcode being damaged and unreadable?

Answer: It is acceptable to place a transparent sticker, used as an ATD, over the 2D Data Matrix, provided that it does not impact its readability (for example if the sticker is reflective), and the Data Matrix does not contain information intended for the patient or included in accordance with the recommendation in Q&A 2.12 (e.g. content previously included in a QR code).

Concerning the human-readable code, the human-readable batch number and expiry date are relevant information for the patient and should remain readable after the pack is opened. Hence, it is not acceptable to place a transparent sticker, used as an ATD, over the human-readable batch number and expiry date if it risks damaging this information when the pack is opened.

1.24. Question: In some cases a medicinal product may carry more than one batch number, typically when the product consists of an active component and a solvent. Which batch number(s) should be encoded in the medicines verification system in that case?

Answer: Only the batch number of the active substance needs to be encoded in the medicines verification system. 10

1.25. Question: When repackaging or re-labelling a pack for the purpose of using it as authorised investigational medicinal product or authorised auxiliary medicinal product according to Article 16(2) of Commission Delegated Regulation (EU) 2016/161, the unique identifier should be decommissioned. What status of decommissioning should the pack have?

Answer: Until there is a specific status for these medicines in the EMVS system, the pack should be decommissioned as "SUPPLIED" when repackaging or re-labelling for use as an authorised investigational medicinal product or authorised auxiliary medicinal product.

1.26. Deleted

1.27. Deleted

1.28. Question: Is there an obligation for direct suppliers to healthcare institutions to offer aggregation services?

Answer: No. The Delegated Regulation does not require hospital suppliers to provide aggregation services. Direct suppliers may however offer the service on a voluntary basis, providing the safeguards outlined in the *Expert Group paper on implementation of the Falsified Medicines Directive in the hospital setting*[4] are met.

[4] https://ec.europa.eu/health/sites/health/files/files/falsified_medicines/2018_hospitalsetting_en.pdf

1.29. Question: Do the unique identifiers of reference and retention samples taken from stock in compliance with Annex 19 of the EU GMP Guidelines[5] and uploaded to the EMVS have to be decommissioned? If yes, to what status?

ANSWER: Yes. In case a pack is taken from a batch and stored as a reference and retention sample after upload to the EMVS it should be decommissioned as "SAMPLE". In general, however, the serial numbers of packs that are taken from a batch and stored as reference and retention samples in order to comply with Annex 19 of the EU GMP Guidelines should not be uploaded in the EMVS. Samples taken voluntarily from a batch by a wholesaler that fall outside of the scope of Annex 19 should be decommissioned as "DESTROYED".

[5] https://ec.europa.eu/health/documents/eudralex/vol-4_en

2. Technical Specifications of the Unique Identifier

2.1. Question: Does Commission Delegated Regulation (EU) 2016/161 limit the length of the unique identifier to 50 characters?

Answer: No. Only the length of the product code, one of the data elements of the unique identifier, is limited to 50 characters.

2.2. Question: Would it be possible to include, on a voluntary basis, a two-dimensional barcode on the packaging of medicinal products for human use not having to bear the safety features if the information carried by the barcode does not serve the purposes of identification and authentication of the medicinal product and does not include a unique identifier?

Answer: Yes, provided that the relevant labelling provisions of Title V of Directive 2001/83/EC are complied with. Examples may include two-dimensional barcodes encoding price indications, reimbursement conditions, etc.

2.3. Is it possible to keep one-dimensional barcodes on the packaging of medicinal products for human use having to bear the safety features, when adding the two-dimensional barcode carrying the unique identifier?

Answer: Yes, provided that the presence of both barcodes does not negatively impact the legibility of the outer packaging. In order to avoid incorrect scanning by end-users, if possible, the barcodes should not be placed in proximity to each other, preferably on different sides of the packaging.

2.4. Question: Is a printing quality of 1.5 according to ISO/IEC 15415 mandatory?

Answer: No. Manufacturers are required to use a printing quality which ensures the accurate readability of the Data Matrix throughout the supply chain until at least one year after the expiry date of the pack or five years after the pack has been released for sale or distribution in accordance with Article 51(3) of Directive 2001/83/EC, whichever is the longer period.

The use of a printing quality of 1.5 or higher gives a presumption of conformity, i.e. manufactures using a printing quality of 1.5 or higher will be presumed to have fulfilled the requirement mentioned in the first paragraph without need to prove that it is actually the case.

If a printing quality lower than 1.5 is used, manufacturers may be asked to prove that requirements mentioned in the first paragraph are met.

2.5. Can manufacturers, on a voluntary basis, place the human readable code on medicinal products with packaging having the sum of the two longest dimensions equal or less than 10 centimetres?

Answer: Yes.

2.6. Are medicinal products with packaging having the sum of the two longest dimensions equal or less than 10 centimetres exempted from bearing the two-dimensional barcode carrying the unique identifier?

Answer: No, Article 7(2) only provides for an exemption from bearing the unique identifier in human readable format. The unique identifier in machine-readable format – the 2D barcode – is still required.

2.7. Question: Is it compulsory to print the national reimbursement number in human-readable format?

Answer: The national reimbursement number or other national number should be printed in human readable format only if required by the national competent authorities of the relevant Member State and not printed elsewhere on the packaging. It should be printed adjacent to the two-dimensional barcode if the dimensions of the packaging allow it, unless national legislation provides otherwise.

2.8. Question: Is it compulsory for the human-readable data elements of the unique identifier to be placed adjacent to the two-dimensional barcode?

Answer: Yes, whenever the dimensions of the packaging allow it.

2.9. Question: What is the smallest font size that can be used to print the unique identifier in human-readable format?

Answer: The font size of the unique identifier should be in accordance with the "Guideline on the readability of the labelling and package leaflet of medicinal products for human use" published in Eudralex – Notice to

Applicants - 2C.
https://health.ec.europa.eu/system/files/201611/2009_01_12_readability_guideline_final_en_0.pdf.

2.10. Question: When encoded in the 2D Data Matrix or printed on the packaging in human-readable format, should the data elements of the unique identifier follow the order laid down in Articles 4(b) or 7(1), respectively, of Commission Delegated Regulation (EU) 2016/161?

Answer: No. Manufacturers can choose the order of the data elements provided that all data elements required by national legislation and Article 4(b) (for the 2D Data Matrix) or Article 7 (for the human-readable format) are present.

2.11. Question: Commission Delegated Regulation (EU) 2016/161 does not mention batch number and expiry date as mandatory components of the human readable code. Is it mandatory to print the batch number and the expiry date in a human-readable format and adjacent to the two dimensional barcode?

Answer: Batch number and expiry date are mandatory components of the labelling of all medicinal products – regardless of whether they bear the safety features – and should be printed on the packaging in accordance with Article 54(h) and (m) of Directive 2001/83/EC. There is no obligation to place batch number and expiry date adjacent to the two dimensional barcode.

2.12. Question: Is it allowed to place a QR code on the packaging of a medicinal product bearing the safety features?

Answer: Commission Delegated Regulation (EU) 2016/161 does not prohibit the placing of a QR code as far as it is not used for the purposes of identification and authentication of medicinal products.

Marketing authorisation holders are however encouraged, wherever technically feasible, to exploit the residual storage capacity of the Data Matrix to include the information they would otherwise include in the QR code (see also Q&A 2.16). This would minimise the number of visible barcodes on the packaging and reduce the risk of confusion as regard the barcode to be scanned for verifying the authenticity of the medicinal product.

Furthermore, in order to avoid incorrect scanning by end-users, if possible, the QR code should not be placed in proximity of the Data Matrix, preferably on a different side of the packaging.

2.13. Question: Where on the packaging should the unique identifier be placed?

Answer: The Delegated Regulation does not specify where on the outer packaging the safety features should be placed. The placement of the safety features is therefore to be supervised by competent authorities in accordance with current practice for labelling requirements.

2.14. Question: Can the graphics on the containers of the medicinal products be printed separately and the Data Matrix added at the final packaging stage - or are there digital printing technologies where all packaging graphics and the UI can be printed in one step?

Answer: The Delegated Regulation does not specify how the safety features should be applied to the outer packaging. The placement of the safety features is therefore to be supervised by competent authorities in accordance with current practice for labelling requirements. The specifics of the technologies used to apply the UI will be for the individual manufacturer to decide and for them to select the most appropriate model suitable for their needs.

According to Annex 16 of the EU GMP Guidelines paragraph 1.7.21, affixing the UI to the packaging of a medicinal product is the responsibility of the Qualified Person. Any outsourcing of this activity to a third party by the manufacturer of the finished medicinal product must be in accordance with the principles described in Chapter 7 of Part I of the EU GMP Guidelines.

2.15. Question: Upon the medicinal product being supplied to the public, the UI is decommissioned and the package is no longer active in the repository. However, the 2D Data

Matrix can still be read-out, for example by a consumer using a smartphone application. Will the possibility to verify the authenticity of the product via the Data Matrix be extended to the end-user (patient)?

Answer: The Delegated Regulation does not provide for verification of the authenticity of the product by the end user. In fact, the verification conducted by the person authorised to supply to the public guarantees that the product is not falsified.

2.16. Question: After the UI data has been encoded, can any residual storage capacity in the Data Matrix be used to store other information?

Answer: The Delegated Regulation states in Article 8 that manufacturers may include information additional to the information contained within the unique identifier in the two-dimensional barcode, where permitted by the competent authority in accordance with article 62 of Title V of the Directive 2001/83/EC. That information should be consistent with the summary of product characteristics, useful for the patient and may not contain promotional elements.

The amount of residual storage capacity of the Data Matrix after the UI data has been encoded will depend upon the size of the Data Matrix as selected by the individual manufacturers responsible for the placing of the UI on the packaging.

2.17. Question: Do human-readable headers (PC, SN, Lot, EXP, NN) have to be placed adjacent to the respective data elements, on the same line, or is some flexibility possible?

Answer: Human-readable headers are not required to be placed adjacent/on the same line as the respective data element. Headers can be placed in any position which allows the unequivocal identification of the human-readable data element.

2.18. Question: For products bearing the human-readable code, is it acceptable to place data elements in multiple locations across the packaging?

Answer: It depends on the data elements and dimensions of the packaging. The product code and serial number should be placed on the same surface, where space allows, so to facilitate manual decommissioning of the unique identifier. Concerning the other data elements, an effort should be made to place them on the same surface as the product code and serial number. Should the packaging dimensions not allow it, however, it is acceptable to place the other data elements as close to the product code and serial number as possible (e.g. adjacent sides).

2.19. Question: Is it acceptable to use a 2D Data Matrix which is rectangular (rather than square) or printed white on black (rather than black on white)?

Answer: Yes. Manufactures can chose to encode the unique identifier in a 2D Data Matrix which is rectangular and/or printed white on black, provided that it fulfils the technical requirement laid down in Article 5 of Commission Delegated Regulation (EU) 2016/161.

2.20. Question: Is it mandatory to include Application/Data Identifiers as part of the human-readable headers or data elements?

Answer: No. Manufacturers can choose whether to include the Application/Data Identifiers as part of the human-readable headers/data elements.

2.21. Question: Is it acceptable to use stickers to place the unique identifier on the outer/immediate packaging?

Answer: As a rule the unique identifier must be printed on the packaging (Article 5(3) of Commission Delegated Regulation (EU) 2016/161).

For medicinal products subject to parallel import and parallel distribution it is possible to use a sticker (adhesive label) provided that the sticker cannot be removed without being damaged and that the sticker fulfils the quality of the printing requirements set out in Article 6 of the Commission Delegated Regulation (EU) 2016/161 (case C-147/20, Novartis Pharma GmbH v Abacus Medicine A/S).

In addition, for medicinal products other than those subject to parallel import and parallel distribution, placing the unique identifier by means of stickers can be accepted in the following circumstances:

- No legal and/or technically feasible alternative exists (e.g. safeguard of trademark rights; glass/plastic immediate packaging without outer packaging; etc.); or
- Competent authorities authorise it due to the marketing authorisation to safeguard public health and ensure continued supply.

The placing/replacement of the unique identifier using stickers must be conducted in accordance with applicable Good Manufacturing Practice principles. Moreover, all applicable labelling requirements in Directive 2001/83/EC must be met and the sticker must not impair the readability of other required labelling elements. The sticker should be tamper-evident, i.e. it should not be possible to remove it without damaging the packaging or the sticker itself or leaving visible signs. The unique identifier should not be printed on a separate sticker to the other labelling particulars unless agreed with the competent authority.

2.22. Question: Do human-readable headers (PC, SN, Lot, EXP, NN) have to comply with the provisions of the QRD-template?

Answer: Yes, preferably. According to the current version of the QRD-template[6], the product code, serial number and national reimbursement number in the human readable code should be preceded by the letters "PC", "SN" and "NN". Batch number and expiry date should follow the abbreviations laid out in Appendix IV of the QRD-template.

[6] https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/product-information requirements/product-information-qrd-templates-human

2.23. Question: Are there specific requirements for the characters used in batch and serial numbers?

Answer: No. However, in order to reduce the risk of false alerts due to end-user scanner misconfigurations, manufacturers are strongly encouraged to follow the recommendations below.

Serial and batch numbers should preferably:

- Contain only uppercase letters;
- Not include special characters (eg. hyphens, question marks, etc.); and
- Avoid the use of the letters "I", "O", "Y" and "Z".

3. General Provision on the Verification and Decommissioning of the Safety Features

3.1. Question: How should the unique identifier be decommissioned if the two-dimensional barcode is unreadable or deteriorated?

Answer: The unique identifier in human readable format should be recorded by any suitable method allowing the subsequent manual querying of the repository system in order to verify and decommission the unique identifier.

3.2. Question: Where the barcode carrying the unique identifier cannot be read, or in case the verification of the unique identifier is temporarily impeded, is it possible to supply the medicinal product to the public?

Answer: Article 30 of Commission Delegated Regulation (EU) 2016/161 prohibits supply to the public if there is reason to believe that the packaging of the medicinal product has been tampered with, or the verification of the safety features of the medicinal product indicates that the product may not be authentic.

In all other cases, the supply of medicinal products to the public is regulated by national legislation.

Without prejudice to national legislation, in the case where it is permanently impossible to read the unique identifier and verify the authenticity of the medicinal product, for example because both the Data Matrix and the human readable code are damaged, it is recommended that the medicinal product is not supplied to the public.

3.3. Question: Can a medicinal product which cannot be authenticated be returned, and to whom? Who should pay for the return?

Answer: Commission Delegated Regulation (EU) 2016/161 does not change the national provisions in place regulating returns of medicines from persons authorised or entitled to supply medicinal products to the public (e.g. pharmacies and hospitals). The regulation of returns of medicinal products, including their financial aspects, remains a national competence.

3.4. Question: Is the use of aggregated codes to simultaneously verify the authenticity of or decommission multiple unique identifiers permitted?

Answer: Recital 20 of the Delegated Regulation gives the possibility of giving aggregated codes allowing the simultaneous verification of multiple Unique Identifiers, provided that the requirements of Commission Delegated Regulation (EU) 2016/161 are complied with.

However, since aggregation is not regulated in the Delegated Regulation any action in that sense from manufacturers/wholesalers/parallel traders (or any actor in the supply chain, for the matter) is only voluntary and needs to be agreed upon by the stakeholders.

3.5. Question: Is it possible to reverse the decommissioned status of a medicinal product that has been physically exported to third countries, when such product is brought back into the EU?

Answer: No. When a medicinal product is physically exported outside of the EU, its unique identifier must be decommissioned in accordance with Article 22(a) of Commission Delegated Regulation (EU) 2016/161. If the exported product is subsequently reimported onto the EU territory (e.g. because it is returned), it is considered an "import" and must be imported by a manufacturing import authorisation (MIA) holder (not a wholesaler) and is subject to the import requirements laid down in Article 51 of Directive 2001/83/EC (batch testing, batch release, etc.). The imported medicinal product should also be given a new unique identifier containing a new batch number and expiry date, if applicable, before it is released for sale and distribution in the EU.

3.6. Question: Can a medicine with only one of the safety features (either the UI or ATD) that has been released for sale before 9 February 2025 remain on the market?

Answer: Yes, a medicine with either a UI or ATD that has been released for sale before the entry into application of the Regulation and has not been repackaged or re-labelled may remain on the market until its expiry date.

3.7. Question: Who should verify and decommission medicines with safety features that are to be used in clinical trials as investigational medicinal products or authorised auxiliary medicinal products?

Answer: According to Articles 16, 23 and 25(4)(c) of Commission Delegated Regulation (EU) 2016/161, the unique identifier on medicines in their commercial presentations bearing safety features should be verified and decommissioned either by manufacturers, wholesalers or persons entitled or authorised to supply to the public before use as authorised investigational medicinal products (IMPs) or authorised auxiliary medicinal products.

For medicines repackaged or relabelled for use in clinical trials, the manufacturer holding the manufacturing and importation authorisation covering IMPs should verify and decommission the unique identifier before they repackage or relabel the medicine.

For medicines that are not repackaged or relabelled, the person entitled or authorised to supply to the public who supplies the medicinal product for subsequent use in a clinical trial should verify and decommission the unique identifier.

In some cases, Member States may require wholesalers to verify and decommission unique identifiers on medicines supplied for clinical trials on behalf of certain entitites under Article 23. 18

4. Verification of the Safety Features and Decommissioning of the unique Identifier by Manufacturers

4.1. Question: Do the records referred to in Article 15 of Commission Delegated Regulation (EU) 2016/161 have to be stored in the repositories system?

Answer: No. The manufacturers can decide how and where to keep the records of every operation he performs with or on the unique identifier.

4.2. Question: Article 18 requires that, in case of suspected falsification or tampering, the manufacturer should inform the competent authorities. Should they also inform the holder of the marketing authorization for the medicinal product?

Answer: Yes, Article 46 of Directive 2001/83/EC requires manufacturers to inform the competent authority and the marketing authorisation holder immediately if they obtain information that medicinal products which come under the scope of their manufacturing authorisation are, or are suspected of being, falsified.

4.3. Question: Articles 18, 24 and 30 of Commission Delegated Regulation (EU) 2016/161 require that manufacturers, wholesalers and persons authorised or entitled to supply medicinal products to the public immediately inform national competent authorities in case of suspected falsification of medicinal products. How should this information be notified by manufacturers?

Answer: It is recommended that manufacturers contact national competent authorities, since the procedure to follow for such notification is a national competence. If they exist, national guidelines should be followed.

4.4. Question: Can a manufacturer use outer packaging carrying a unique identifier which has been placed by a packaging materials provider?

Answer: Yes. Art. 14 of Commission Delegated Regulation (EU) 2016/161 requires that the manufacturer responsible for placing the safety features on the medicinal product verifies that the two-dimensional barcode carrying the unique identifier complies with Articles 5 and 6 of the said Regulation, is readable and contains the correct information before releasing the medicinal product for sale and distribution.

Where pre-printed cartons are used, the outsourcing of the pre-printing of the UI to a packaging material provider should be done in accordance with Chapter 7 of Part I of the EU GMP Guidelines, including the signature of a written agreement among the parties establishing the corresponding responsibilities. The packaging materials provider should be audited and qualified.

The manufacturer releasing the product for sale and distribution (see Q&A 7.13) should verify the capacity of the contracted packaging materials provider to perform the task in accordance with the requirements of the Regulation and in compliance with applicable GMP. Upon receipt of the pre-printed packaging materials, the manufacturer of the finished medicinal product is expected to perform appropriate checks on the quantity and quality of the UIs in line with EU-GMP principles.

4.5. Question: Are manufacturers responsible for ensuring unique identifiers are readable and complete?

Answer: Yes. Manufacturers must check that the 2D barcode is readable and contains the correct information (Article 14 of Commission Delegated Regulation (EU) 2016/161).

Furthermore, manufacturers must work closely with marketing authorisation holders to ensure that all relevant information on unique identifiers has been uploaded correctly to the repository system and corresponds to the information encoded in the unique identifier before they release medicines for sale or distribution (Article 33(2) of Commission Delegated Regulation (EU) 2016/161).

4.6. Question: Can a manufacturer outsource the placing of the safety features on a packaged medicinal product to another manufacturer?

Answer: Yes. The outsourcing of the placing of the safety features on a packaged medicinal product can be contracted to another manufacturer in line with Chapter 7 of Part I of the EU GMP Guidelines, as long as they have a manufacturing authorisation (MIA). The contracting manufacturer must also make a statement confirming compliance with Annex 16 Appendix 1 of the EU GMP Guidelines available to the Qualified Person certifying the final product. The contracted manufacturer must be included in the marketing authorisation.

5. Verification of the Safety Features and Decommissioning of the unique Identifier by Wholesalers

5.1. Question: How should the expression "the same legal entity" referred to in Articles 21(b) and 26(3) of Commission Delegated Regulation (EU) 2016/161 be interpreted?

Answer: This expression should be interpreted in accordance with national legislation. As general guidance, and without prejudice to national legislation, a legal entity may be considered the same when, for example, it has the same registration number in the national company registry or, if no national registration is required, the same number for tax purposes (i.e. VAT number).

5.2. Question: Member States may hold stocks of certain medicinal products for the purpose of public health protection. How should the unique identifiers on those products be verified and decommissioned?

Answer: In accordance with Article 23(f) of the Delegated Regulation, Member States may request wholesalers to verify the safety features of and decommission the unique identifier of medicinal products which are supplied to governmental institutions maintaining stocks of medicinal products for the purposes of civil protection and disaster control.

5.3. Question: Articles 18, 24 and 30 of Commission Delegated Regulation (EU) 2016/161 require that manufacturers, wholesalers and persons authorised or entitled to supply medicinal products to the public immediately inform national competent authorities in case of suspected falsification of medicinal products. How should this information be notified by wholesalers?

Answer: It is recommended that wholesalers contact national competent authorities, since the procedure to follow for such notification is a national competence. If they exist, national guidelines should be followed.

5.4. Question: Articles 20, 21 and 22 require wholesalers to verify the authenticity and/or decommission the unique identifier only. Do wholesalers need to verify the integrity of the anti-tampering device when complying with those Articles?

Answer: No, wholesalers do not need to (but can) verify the integrity of the anti-tampering device when complying with Articles 20, 21 and 22.

5.5. Question: Article 22(a) requires a wholesaler to verify the authenticity of and decommission the unique identifier of all medicinal products they intend to distribute outside of the Union. Is it necessary to decommission the unique identifier if the medicinal product is sold to a party established outside the EU but that product does not physically leave the wholesaler's premises in the EU?

Answer: No. The purpose of Article 22(a) is to ensure the decommissioning of unique identifiers on packs which leave the EU territory, in order to avoid that those active codes may be harvested by traffickers. In case the medicinal product is sold to a party established outside the EU but physically remains in the wholesaler's premises in the EU, the unique identifier on the product should not be decommissioned. If that medicinal

product is subsequently imported (while physically remaining in the EU) by a holder of a manufacturing and import authorisation (a wholesaler cannot import medicinal products), no action from the wholesaler physically holding the product is required with regard to the safety features.

5.6. Question: Do wholesalers have the obligation to decommissioning the unique identifier of a medicinal product when they sell the product "business-to-business" to a company which buys it for the purpose of research?

Answer: Article 23(g) allows the decommissioning by wholesalers of medicinal products supplied for the purpose of research, except when supplied to healthcare institutions. Although the Article does not explicitly mention that it applies to the supply of products for the purpose of research to companies which are not universities or other higher education establishments, it is desirable to include such a case in the scope of this Article (provided that those companies are not healthcare institutions) in order to guarantee the decommissioning of the unique identifiers on those products.

5.7. Question: Is wholesale distribution of medicinal products with a damaged/unreadable 2D Data Matrix code allowed, if there is no suspicion of falsification?

Answer: It depends on the human readable code. If the verification of the authenticity of the unique identifier (UI) can be performed using the human readable code, the product can be further distributed.

If the verification of the authenticity of the UI cannot be performed (because the human readable code is damaged or absent), then the wholesaler should not further distribute the product with unreadable codes (Article 24 of Regulation No 2016/161). This requirement is independent of whether the verification was mandatory under Article 20 of Commission Delegated Regulation (EU) 2016/161 or voluntarily performed by wholesalers.

5.8. Question: Can a wholesaler request another wholesaler to verify the authenticity and decommission the unique identifiers for medicinal products they intend to distribute outside the EU on their behalf?

No. According to Article 22(a), the wholesaler who physically holds the medicinal products and intends to distribute these products outside the EU must verify their authenticity and decommission the unique identifiers. This obligation cannot be delegated to another wholesaler, as the audit trail would not reflect the reality of the supply chain, as required by Article 35(1)(g) of the Regulation.

5.9. Deleted

5.10. Question: How can a wholesalers be sure that medicines they receive without safety features have been batch released prior to the entry into application of the safety features (9 February 2019)?

According to Commission Delegated Regulation (EU) 2016/161, marketing authorisation holders and manufacturers may only place medicines released before 9 February 2019 on the EU market without safety features. In principle this means that products on the EU market without safety features must have been released before the entry into application of the safety features.

Wholesalers may request that manufacturers include the batch release date in the delivery note of non-serialised medicines in order to confirm that the medicines were released before the safety features became mandatory.

5.11. Question: Should wholesalers be connected to the national repositories or can they be connected to the European hub?

A wholesaler physically holding products and performing activities related to wholesale outlined in Articles 20-23 Commission Delegated Regulation (EU) 2016/161 (such as the 22 verification of returns or decommissioning for export) should be connected to and perform operations in the national repository where the activities take place. A connection to the national system is necessary to ensure that the the audit trail is accurate and complete.

5.12. Question: Is it possible for a wholesaler with multiple locations to use a single NMVO connection and account to verify and decommission medicines?

Answer: No. In order to ensure compliance with Articles 13 and 35(1)(g) of Commission Delegated Regulation (EU) 2016/161, each physical location of the wholesaler must be uniquely identifiable when connecting to the NMVS and performing operations in the system.

5.13. Question: According to Article 20(b) Commission Delegated Regulation (EU) 2016/161, wholesalers must verify medicinal products they do not receive from the manufacturer, marketing authorisation holder or wholesalers designated by the marketing authorisation holder. Is it necessary to verify the unique identifier of medicinal products sent directly from the manufacturer but purchased from a wholesaler who is neither the manufacturer, marketing authorisation holder or designated by the marketing authorisation holder?

Answer: No. The exemption in Article 20(b) refers to the physical transfer of medicines. Even if they have been purchased from a third party, medicines that have been shipped directly from the manufacturer, marketing authorisation holder or a designated wholesaler do not need to be verified in accordance with Article 20(b).

5.14 Is it allowed to verify the authenticity of the UI when the product is not in physical possession?

Answer: Yes, but only as an additional check to Article 20 of Commission Delegated Regulation (EU) 2016/161.

Article 20 of that Regulation requires wholesalers to verify the authenticity of the Unique Identifier (UI) for *at least* the medicinal products in *his physical possession* the referred to in this Article, i.e.:

(a) medicinal products returned to him by persons authorised or entitled to supply medicinal products to the public or by another wholesaler;

(b) medicinal products he receives from a wholesaler who is neither the manufacturer nor the wholesaler holding the marketing authorisation nor a wholesaler who is designated by the marketing authorisation holder, by means of a written contract, to store and distribute the products covered by his marketing authorisation on his behalf.

This obligation is a minimum requirement. Therefore, a wholesaler may verify the authenticity of other products of other origins than those addressed in Article 20 via the UI when the product is not in physical possession. Such practice should be considered an additional check.

It does exempt from the obligation to verify the UI once the product is in physical possession and can thus not replace it.

In this context, it should be stressed that only authorised suppliers located in the EU can put medicinal products on the market in the EU. Verifying the UI of packs located outside the EU does not replace import testing and batch certification after import by authorised manufacturers.

6. Verification of the Safety Features and Decommissioning of the unique Identifier by Persons Authorised or entitled to supply Medicinal Products to the Public

6.1. Question: In-patients in a hospital may be administered medicinal products during their stay, the costs of which may be charged to their insurer, which constitutes a sale. In this case, would the hospital (or any other healthcare institution) be allowed to verify the safety features and decommission the unique identifier of those products earlier than the time of supply to the public, in accordance with Article 25(2)?

Answer: Yes. In the case described, the charging of the medicinal products costs to the patient's insurer happens as a consequence of the administration of that product to the patient (regardless of whether the sale

takes place before or after the actual administration). Consequently, it is considered that the charging of the cost of the medicinal product to the patient's insurer (or to the patient himself, for the matter) does not preclude hospitals from applying the derogation provided for in Article 25(2).

6.2. Question: How should the expression "the same legal entity" referred to in Articles 21(b) and 26(3) of Commission Delegated Regulation (EU) 2016/161 be interpreted?

Answer: See Q&A 5.1.

6.3. Question: Many hospitals and other healthcare institutions supply the contents of packages of a medicinal product to more than one patient. Where only part of a pack of a medicinal product is supplied, when should the decommissioning of the unique identifier be performed?

Answer: The unique identifier should be decommissioned when the packaging is opened for the first time, as required by Article 28 of Commission Delegated Regulation (EU) 2016/161.

6.4. Question: Does automated dose dispensing require the placing of new safety features on the individual patient doses/packs?

Answer: No. Automated dose dispensing falls in the scope of Article 28 of Commission Delegated Regulation (EU) 2016/161. Consequently, it is not necessary to place new safety features on the individual patient's dose/pack.

6.5. Question: Is it possible for the wholesaler to scan the unique identifiers (UI) in a consignment before shipping the consignment to a hospital, store the UI information and then, once the hospital received the consignment, decommission the UIs using the stored information following an explicit request by the hospital?

Answer: No, the above process is not in line with the provisions of Commission Delegated Regulation (EU) 2016/161:

- Since the decommissioning would happen through the wholesaler's computer using the wholesaler's log-in ID, the decommissioning operation would be recorded in the system and in the audit trail as an operation performed by the wholesaler, and not by the hospital. This is not acceptable as the audit trail would not reflect the reality of the supply chain, as required by Article 35(1)(g) of the Regulation.

- Articles 23 and 26 of Commission Delegated Regulation (EU) 2016/161 are explicit about those cases where wholesalers are entitled to decommission the safety features on behalf of hospitals. Decommissioning on behalf of hospitals under other circumstances is therefore not allowed.

6.6. Question: Is it acceptable for hospitals/hospital pharmacies to subcontract their decommissioning obligations to wholesalers?

Answer: No. However, there are possible scenarios, compatible with Commission Delegated Regulation (EU) 2016/161, where wholesalers (including manufactures supplying their own products by wholesale) could facilitate the decommissioning operation of hospitals (illustrative examples only, list not exhaustive):

- Wholesalers could scan the packs in the hospital consignment to acquire the information on the UIs and encode such information into an aggregated code. Decommissioning would then be performed by the hospital by scanning the aggregated code. The only equipment needed for this operation would be a hand-held scanner and a computer (connected to the national repository).

- Wholesalers could acquire the information on the UIs in the hospital consignment and make this information available to the hospital, by secure means. The hospital would then use such information to perform the decommissioning (without having to physically scan the packs).

6.7. Question: Articles 18, 24 and 30 of Commission Delegated Regulation (EU) 2016/161 require that manufacturers, wholesalers and persons authorised or entitled to supply medicinal products

to the public immediately inform national competent authorities in case of suspected falsification of medicinal products. How should this information be notified by persons authorised or entitled to supply medicinal products to the public?

Answer: It is recommended that persons authorised or entitled to supply medicinal products to the public contact national competent authorities, since the procedure to follow for such notification is a national competence. If they exist, national guidelines should be followed.

6.8. Question: For persons authorised or entitled to supply medicinal products to the public operating within a healthcare institution, must the verification of the integrity of the anti-tampering device be done at the same time as the verification and decommissioning of the unique identifier?

Answer: No. Article 25(2) of Commission Delegated Regulation (EU) 2016/161 outlines that verification of the safety features can be done at any time a medicine is in the physical possession of a healthcare institution as long as no sale takes place between delivery to the healthcare institution and supply to the public. Therefore, decommissioning of the UI and verification of the ATD can be done separately before supply to the public.

6.9. Question: Is it possible for a pharmacy chain with multiple locations to use a single NMVO connection and account to verify and decommission medicines in different branches before dispense?

Answer: No. In order to ensure compliance with Articles 13 and 35(1)(g) of Commission Delegated Regulation (EU) 2016/161, each physical location of a pharmacy chain must be uniquely identifiable when connecting to the NMVS and performing operations in the system.

7. Establishment, Management and Accessibility of the Repositories System

7.1. Question: How should the expression "manufacturers of medicinal products bearing the safety features", as used in Commission Delegated Regulation (EU) 2016/161, be interpreted?

Answer: For the purposes of Commission Delegated Regulation (EU) 2016/161, "manufacturer" means the holder of a manufacturing authorisation in accordance with Article 40 of Directive 2001/83/EC. The expression "manufacturers of medicinal products bearing the safety features" encompasses any holder of the said authorisation performing partial or total manufacture of a medicinal product bearing the safety features.

7.2. Question: Article 31 of Commission Delegated Regulation (EU) 2016/161 allows wholesalers and persons authorised or entitled to supply medicinal products to the public to participate in the legal entity/ies setting up and managing the repositories system, at no costs. Can the terms of such participation be regulated by stakeholders, for examples through the statutes of establishment or incorporation of the legal entity/ies?

Answer: Yes, it is possible, provided that the terms do not contradict what is enshrined in legislation. In case of discrepancy, the provisions of Commission Delegated Regulation (EU) 2016/161 and Directive 2001/83/EC prevail.

7.3. Deleted.

7.4. Question: How should the expressions "application programming interface" or "graphical user interface" referred to in Articles 32(4) and 35(1) of Commission Delegated Regulation (EU) 2016/161 be interpreted?

Answer: The expression "application programming interface" refers to a software/software interface consisting of a set of programming instructions and standards used by a piece of software to ask another piece of software to perform a task. The programming instructions and standards are set by the software being called upon. In the context of Commission Delegated Regulation (EU) 2016/161, the expression refers to the programming instructions and standards allowing the software of persons authorised or entitled to supply medicines to the public, wholesalers and national competent authorities to query the repository system.

The expression "graphical user interface" (GUI) refers to a human/computer interface that allows users to interact with software or a database through graphical icons and visual indicators without the need of using complex programming language.

The purpose of Article 35(1)(i) is to ensure that, in case of software failure, wholesalers and persons authorised/entitled to supply medicines to the public have an alternative way to connect to the national medicine verification system to verify the authenticity of/decommission the unique identifier. However, to avoid that wholesalers and persons authorised/entitled to supply medicines to the public rely routinely on the GUI to verify the authenticity of/decommission the unique identifiers on their products, Article 35(1)(i) limits the circumstances in which they are entitled (i.e. have the legal right) to use the GUI to the case of failure of their own software. The use of the GUI in any other circumstance is not prohibited but is subject to the agreement of the national medicine verification organisation owning the GUI. See also Q&A 7.18.

7.5. Question: Article 33(1), second subparagraph, requires that information referred to in paragraphs 2(a) to 2(d) of that article, with the exception of the serial number, is stored in the hub. Does this mean that the serial number cannot be uploaded to the hub?

Answer: No, the provision only regulates which information is to be stored in the hub.

7.6. Question: Articles 34(4), 35(4) and 36(n) refer to the linking of the information on unique identifiers removed or covered to the information on the equivalent unique identifiers placed for the purposes of complying with Article 47a of Directive 2001/83/EC. Is the linking required to be at the level of individual unique identifiers? How does the linking work in practice?

Answer: No, it is not necessary to link individual unique identifiers. The link can be made at batch level by linking the list of decommissioned unique identifiers in the "old" batch (the batch to be repacked/relabelled) and the list of new unique identifiers placed on packs in the "new" batch (the repacked batch). The provision does not require the linking to be done at the level of individual unique identifiers, since the number of packs in the batch to be repacked/relabelled (and consequently the number of unique identifiers in that batch) may not correspond to the number of packs (and of unique identifiers) in the new batch – making a one-to-one link between unique identifiers impossible.

7.7. Question: In Article 35(1)(f), does the upper limit of 300 ms for a repository to respond to queries also apply when multiple repositories are implicated in the query, for example in case of cross-border verification?

Answer: 300 ms is the maximum response time of an individual repository. When the verification/ decommissioning operation requires the querying of multiple repositories in the repositories system, for example in case of inter-market transactions, the maximum response time is obtained by multiplying the maximum response time of an individual repository (300 ms) by the number of repositories involved in the query – for example, the maximum response time for a query involving national repository A, the hub, and national repository B would be 900 ms.

It should be noted that the system response time does not include the time needed by the query data to move from one repository to the other (which depends from the speed of the internet connection).

7.8. Question: How will the identity, role and legitimacy of the users of the repository system be verified?

Answer: It is the responsibility of the legal entity establishing and managing a repository to put in place appropriate security procedures ensuring that only verified users, i.e. users whose identity, role and legitimacy has been verified, are granted access to that repository.

7.9. Question: In Article 38(1), does the sentence "with the exception of the information referred to in Article 33(2)" refer to data access only, or also to data ownership?

Answer: It refers to data access only.

7.10. Question: In Article 38(1), what is the meaning of "information on the status of the unique identifier"?

Answer: The information on the status of the unique identifier includes whether the unique identifier is active or decommissioned, and in the latter case, the reasons for the decommissioning.

7.11. Question: What is the purpose of the exceptions laid out to in the second sentence of Article 38(1) concerning access to the information referred to in Article 33(2) and the information on the status of a unique identifier?

Answer: Article 38 of Commission Delegated Regulation (EU) 2016/161 regulates the ownership and the access of the data stored in the repositories system. It lays down the general rule and an exception to that rule. Since the purpose of Article 38 is, inter alia, to protect the confidentiality of data in the repositories system, including commercially confidential data, as required by Article 54a(3)(b) and (c) of Directive 2001/83/EC, the exception should be interpreted narrowly. In particular, the use of the exception should be limited to those cases where access to the data is necessary to perform the verification/decommissioning operations required by Commission Delegated Regulation (EU) 2016/161, as explained in recital 38.

7.12. Question: Is it possible to have multiple national repositories, multiple supranational repositories or a combination of national and supranational repositories serving the territory of a given Member State?

Answer: No. In accordance with Article 32, paragraphs 1 and 2, the territory of a given Member State should be served by the hub and either a national or a supranational repository connected to the hub.

7.13. Question: For the purposes of the application of Articles 33 and 48 of Commission Delegated Regulation (EU) 2016/161, what is understood for 'medicinal products that have been released for sale or distribution'?

Answer: The text 'medicinal products that have been released for sale or distribution' refer to products which have been batch released in accordance with Article 51 of Directive 2001/83/EC. According to Annex 16 of the EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use "Certification by a Qualified Person (QP) and Batch Release", the process of batch release comprises of:

i. The checking of the manufacture and testing of the batch in accordance with defined release procedures.
ii. The certification of the finished product batch performed by a QP signifying that the batch is in compliance with GMP and the requirements of its MA. This represents the quality release of the batch.
iii. The transfer to saleable stock, and/or export of the finished batch of product which should take into account the certification performed by the QP. If this transfer is performed at a site other than that where certification takes place, then the arrangement should be documented in a written agreement between the sites.

Therefore, medicinal products that have been certified for release by a QP without including the safety features in their packaging before the entry into application of the Regulation, may be placed on the market, distributed and supplied to the public until their expiry date.

7.14. Question: How should the expression "marketing authorisation holder", as used in Commission Delegated Regulation (EU) 2016/161, be interpreted?

Answer: The term "marketing authorisation holder" is used in Commission Delegated Regulation (EU) 2016/161 to indicate holders of marketing authorisations in the sense of Article 6 of Directive 2001/83/EC.

7.15. Question: Are parallel importers/distributors required to comply with Article 33(1) and upload the information in Article 33(2) into the repository system? Should they also upload a list of designated wholesalers?

Answer: Parallel traders are obliged to comply with Article 33 and upload in the repositories system in the following two cases:

- If they hold a marketing authorisation in the sense of Article 6 of Directive 2001/83/EC, in which case they may also upload the list of wholesalers they have designated in accordance with Article 20(b) of Commission Delegated Regulation (EU) 2016/161; or

- If they repack/relabel and place new safety features or replace safety features in accordance with Article 47a of Directive 2001/83/EC on the medicinal products they supply. In this case, parallel traders who do not hold a marketing authorisation in the sense of Article 6 of Directive 2001/83/EC may not designate their own wholesalers and should not upload a list of wholesalers into the repository system.

Parallel traders who repack/relabel their products and place new safety features or replace safety features in accordance with Article 47a of Directive 2001/83/EC on the medicinal products they supply have to comply with Articles 33, 40 and 42 of Commission Delegated Regulation (EU) 2016/161 as they are considered the "persons responsible for placing those medicinal products on the market" in that Member State.

7.16. Question: In accordance with Article 33(1), the information laid down in Article 33(2) must be uploaded in the repositories system before the product is released for sale and distribution. Does this mean that the upload needs to take place before the Qualified Person (QP) performs the batch certification and thus the safety feature information relative to any manufacturing waste should also be uploaded in the system?

Answer: No. The information laid down in Article 33(2) of Commission Delegated Regulation (EU) 2016/161 needs to be present in the system at the time the batch is released for sale and distribution (see Q&A 7.13 for what is understood for *released for sale or distribution*). It is acceptable to upload that information at such a time that the system is not burdened with information relative to manufacturing waste, i.e. (parts of) manufactured batches that have not been certified, provided that the upload takes place before the medicinal product is transferred to saleable stock.

7.17. Question: Does Article 37(d) require that a national medicine verification organisation (NMVO) directly alerts the relevant national competent authorities, the EMA and the Commission about a falsification? Is there is a time limit for such alerting?

Answer: The use of the term "provide for" in Article 37(d) of Commission Delegated Regulation (EU) 2016/161 means that an NMVO has to ensure that the national competent authorities, the EMA[7] and the Commission[8] are informed. The NMVO can fulfil this obligation either directly or by ensuring this task is performed by someone else.

The NMVO should ensure authorities are informed as soon as it is clear that the alert triggered in accordance with Article 36(b) cannot be explained by technical issues with the repositories system, the data upload, the person performing the verification or similar technical issues. 30

7.18. Question: Does Article 35(1)(i) of Commission Delegated Regulation (EU) 2016/161 prohibit wholesalers and persons authorised or entitled to supply medicinal products to the public from using the national medicine verification system's graphical use interface (GUI) to verify/decommission the unique identifiers on their products when their own software is not broken?

Answer: No. The use of the GUI by wholesalers and persons authorised/entitled to supply medicines to the public in circumstances other than the failure of their own software is not prohibited but is subject to the agreement of the national medicine verification organisation owning the GUI (in the absence of entitlement, the agreement of the system owner is necessary). See also Q&A 7.4.

[7] By email to QDEFECT@ema.europa.eu
8 By email to SANTE-PHARMACEUTICALS-B4@ec.europa.eu

7.19. Question: Can a marketing authorisation holder delegate the uploading of the information laid down in Article 33(2) of Commission Delegated Regulation (EU) 2016/161?

Answer: Yes. Marketing authorisation holders (MAHs) may delegate the uploading of the information laid down in Article 33(2) to third parties (on-boarding partners (OBPs)) by means of a written agreement between both parties. The MAH remains legally responsible for these tasks.

In all cases, the MAH must ensure with a high level of confidence the accuracy, confidentiality and integrity of the data uploaded into the system. This includes, but is not limited to: procedures to ensure that uploaded data and actual batch properties correspond (such as, batch number, expiry dates, destination market, batch size), procedures for secure data exchange with the subcontractor and procedures to ascertain that data to be uploaded has not been corrupted in any way. Data uploading performed by means of infrastructures, hardware and software that are physically located outside the EEA is strongly discouraged.

7.20. Question: What is meant by *investigation* of all potential incidents of falsification flagged in the system in Article 37(d) of Commission Delegated Regulation (EU) 2016/161?

Answer: The purpose of the investigation in Article 37(d) is to rule out that alerts triggered in the system have been caused for technical reasons, such as issues with the repository system, data upload, data quality, incorrect end-user scanning or other similar technical issues.

As outlined in Q&A 7.17, national competent authorities, EMA and the European Commission should be informed as soon as it is clear that alert cannot be explained by technical reasons. On the basis of the information received, an investigation into the falsification incident will be launched by the authorities in line with European and national procedures.

7.21 Question: Should NCAs have access to all end-user information in the audit trail, including the names and addresses of end-users in another Member State?

Answer: Yes, all NCAs shall have full access to all audit trail data upon request. This includes information such as the corporate name and address of wholesalers and persons authorised or entitled to supply medicinal products to the public, who are involved in verifying the authenticity and decommissioning of a unique identifier.

8. Obliations of Marketing Authorisation Holders, parallel Importers and parallel Distributors

8.1. Question: Can marketing authorization holders delegate the performing of their obligations under Articles 40 and 41 to a third party?

Answer: Marketing authorisation holders can (but are not obliged to) delegate part of their obligations under Articles 40 and 41 to a third party by means of a written agreement between both parties. However, marketing authorisation holders remain legally responsible for those tasks.

In particular, marketing authorisation holders can delegate the performing of their legal obligation under Article 40(a) and 40(b), as well as the decommissioning task in referred to in Article 41.

8.2. Question: Situations arise where, for the same batch of product, competent authorities from different Member States issue different levels of recall, e.g. patient level *vs* wholesaler level, or no recall at all. How will Article 40 of Commission Delegated Regulation (EU) 2016/161 work in this type of scenario?

Answer: Article 40 of Commission Delegated Regulation (EU) 2016/161 would not apply to recalls at patient level as the scope of the Delegated Regulation does not extend beyond the supply of the medicinal product to the end consumer. Where a medicinal product is recalled at pharmacy level in a Member State and at wholesale level in another, the marketing authorisation holder should customise the information they need to provide in the relevant national/supranational repositories in accordance with Article 40(c).

8.3. Question: Certain Member States have national systems managing recalls and withdrawals of medicinal products in place. Would it be possible to interface those national systems with the repositories system for the verification of the safety features?

Answer: Commission Delegated Regulation (EU) 2016/161 does not provide for the connection between the national systems for recalls/withdrawal of medicinal product and the repositories system. Such connections may be considered by the legal entities managing the relevant repositories in the repositories system, on a voluntary basis.

8.4. Question: Are parallel importers/distributors required to comply with Articles 40 and 42 of Commssion Delegated Regulation (EU) 2016/161?

Answer: Parallel traders are obliged to comply with Articles 40 and 42 of Commission Delegated Regulation (EU) 2016/161 in the following two cases:

- If they hold a marketing authorisation in the sense of Article 6 of Directive 2001/83/EC.

- If they repack/relabel and place new safety features or replace safety features in accordance with Article 47a of Directive 2001/83/EC on the medicinal products they supply.

Parallel traders who repack/relabel their products and place new safety features or replace safety features in accordance with Article 47a of Directive 2001/83/EC on the medicinal products they supply have to comply with Articles 33, 40 and 42 of Commission Delegated Regulation (EU) 2016/161 as they are considered the "persons responsible for placing those medicinal products on the market" in that Member State.

8.5. Question: In the case of free samples which are obliged by national law to include in their labelling the sentence "Free sample. Not to be sold", can the obligation to bear the safety features be waived?

Answer: No. Article 41 of Commission Delegated Regulation (EU) 2016/161 requires that marketing authorisation holder intending to supply any of his medicinal products as a free sample shall, where that product bears the safety features, indicate it as a free sample in the repositories system and ensure the decommissioning of its unique identifier before providing it to the persons qualified to prescribe it. Consequently, free samples are in the scope of the Regulation and have to bear the safety features.

8.6. Question: Can marketing authorisation holders upload in the repositories system serial numbers that are never actually used as data elements of unique identifiers?

Answer: No. The purpose of the repository system is to the information on the safety features is contained. Serial numbers that are not actually used as data elements in unique identifiers should not be uploaded and stored in the repositories system as they represent a security risk for the system.

8.7. Question: What are the obligations of operators who supply medicinal products on the ground of Article 126a (Cyprus clause) with regard to the safety features?

Answer: The term "marketing authorisation holder" is used in Commission Delegated Regulation (EU) 2016/161 and in Directive 2001/83/EC to indicate holders of marketing authorisations in the sense of Article 6 of the said Directive. Hence, the term does not apply to operators who distribute medicinal products on the ground of Article 126a. However, in order to handle medicinal products, those legal entities have to have a manufacturing authorisation and/or a wholesale distribution authorisation and/or a parallel import license. They are therefore subject to the obligations laid down in Commission Delegated Regulation (EU) 2016/161 for manufacturers and/or wholesale distributors and/or parallel importers/distributors.

In addition, should those operators place or replace the safety features in accordance with Article 47a of Directive 2001/83/EC on the medicinal products they supply, they need to comply with Articles 33, 40 and 42 of Commission Delegated Regulation (EU) 2016/161 as they are the "person responsible for placing those medicinal products on the market" in the Member State for which an authorisations in the sense of Article 126a was granted.

8.8. Question: In the case of replacement of the safety features by parallel traders, can the decommissioning of the original unique identifier be carried out by the wholesaler from whom they receive the product?

Answer: No. The decommissioning of the original unique identifier must be performed by the parallel trader holding the manufacturing authorisation and replacing the safety features (Article 16 of Commission Delegated Regulation (EU) 2016/161).

8.9. Question: Should marketing authorisation holders upload the unique identifiers for products with 2D barcodes released for sale or distribution before the date of application of Commission Delegated Regulation (EU) 2016/161??

Answer: Yes. According to Article 48 of Commission Delegated Regulation (EU) 2016/161, medicines released for sale or distribution before the date of application of this Regulation without a unique identifier may remain on the EU market until their expiry date, as long as they are not repackaged or relabelled after that date. If they are repackaged or relabelled after the date of application of this Regulation, the manufacturer must place safety features in accordance with Directive 2001/83/EC and Commission Delegated Regulation (EU) 2016/161.

This transitional measure does not apply for products which were released before the date of application of this Regulation with a unique identifier. The unique identifiers for such products should be uploaded to the system before the entry into application of the new rules. This should help to avoid alerts for genuine products released before the date of application of this Regulation due to lack of data in the repository.

9. Lists of Derogations and Notifications to the Commission

9.1. Question: Can marketing authorisation holders submit their proposals for amendments to Annex I of Commission Delegated Regulation (EU) 2016/161 to the Commission?

Answer: Only Member States notifications are taken into account for the purpose of establishing Annex I and II of the Delegated Regulation, in accordance with Article 54a(2)(c) of Directive 2001/83/EC. Concerning Annex I, Member States may inform the Commission of medicinal products which they consider not to be at risk of falsification (Article 54a(4) of Directive 2001/83/EC).

10. Transitional Measures and Entry into Force [DELETED]

10.1. Deleted

11. Annex I

11.1. Question: How should the term "Kits" referred to in Annex I to Commission Delegated Regulation (EU) 2016/161 be interpreted?

Answer: The term "kit" is defined in Article 1(8) of Directive 2001/83/EC. It refers to "any preparation to be reconstituted or combined with radionuclides in the final radiopharmaceutical, usually prior to its administration".

11.2. Question: Are fat emulsions used for parenteral nutrition and having an ATC code beginning with B05BA exempted from bearing the safety features?

Answer: Yes. Fat emulsions having an ATC code beginning with B05BA are included in the category "solutions for parenteral nutrition" listed in Annex I to Commission Delegated Regulation (EU) 2016/161. Such emulsions are therefore exempted from the obligation to bear the safety features.

12. Annex II

12.1. Question: Are over-the-counter omeprazole products formulated as gastro-resistant tablets in the scope of Annex 2 and therefore required to bear the safety features?

Answer: No. Only over-the-counter medicinal products containing omeprazole 20 or 40 mg formulated as hard gastro-resistant capsules have to bear the safety features, as the two reported incidents of falsification that led to certain omeprazole products being added to Annex II concerned that specific pharmaceutical form of omeprazole.

2. European Commission (EU) – Questions and Answers on Importation of APIs

1. QUESTION: WHEN DO THE NEW RULES FOR THE WRITTEN CONFIRMATION APPLY?
Answer: They apply as of 2 July 2013. Any active substance imported into the EU from that date is subject to the rules on the written confirmation.

2. QUESTION: DO THE RULES ON THE WRITTEN CONFIRMATION ALSO APPLY TO ACTIVE SUBSTANCES FOR VETERINARY MEDICINAL PRODUCTS?
Answer: No. The rules apply only to active substances for medicinal products for human use.

2A. QUESTION: DO THE RULES ON THE WRITTEN CONFIRMATION ALSO APPLY TO BLOOD PLASMA?
Answer: No. However, processed derivatives of plasma having a pharmacological, immunological or metabolic action are considered as active substance and written confirmation is thus required.

3. QUESTION: DO THE RULES ON THE WRITTEN CONFIRMATION APPLY TO ACTIVE SUBSTANCES FOR MEDICINAL PRODUCTS INTENDED FOR RESEARCH AND DEVELOPMENT TRIALS?
Answer: Active substances imported to be used in the manufacture of non-authorised medicinal products intended for research and development trials are excluded from the rules.
Active substances imported to be used in the manufacture of authorised medicinal products intended for research and development trials are expected to fulfil the requirements of Directive 2001/83/EC and be accompanied by a written confirmation, unless there is proof that the full amount of the imported API will be used for the manufacture of batches/units of an authorised medicinal product exclusively intended for research and development trials. In the latter case, those batches/units of an authorised medicinal product fall outside the scope of Directive 2001/83/EC and the API used in their manufacture is exempted from the rules on the written confirmation.

4. QUESTION: DO THE RULES ON THE WRITTEN CONFIRMATION APPLY TO ACTIVE SUBSTANCES WHICH ARE BROUGHT INTO THE EU WITHOUT BEING IMPORTED ('INTRODUCED' ACTIVE SUBSTANCES)? AN EXAMPLE IS THE INTRODUCTION OF AN ACTIVE SUBSTANCE WHICH IS SUBSEQUENTLY EXPORTED.
Answer: No. The rules on the written confirmation only apply to the *import* of active substances for medicinal products for human use.

5. QUESTION: WHAT IF, AT THE TIME OF EXPORT OF AN ACTIVE SUBSTANCE TO THE EU, IT IS NOT KNOWN WHETHER THE ACTIVE SUBSTANCE IS USED IN A MEDICINAL PRODUCT FOR HUMAN USE OR NOT?
Answer: If the consignment is not accompanied by a written confirmation, the active substance cannot be used in a medicinal product for human use.

6. QUESTION: IS THE WRITTEN CONFIRMATION EXPECTED TO CONFIRM COMPLIANCE WITH EU-RULES?
Answer: No. The written confirmation has to confirm compliance with GMP rules 'equivalent' to the rules applied in the EU.

7. QUESTION: IN MY NON-EU COUNTRY, THE APPLICABLE STANDARDS FOR MANUFACTURING OF ACTIVE SUBSTANCES ARE THE GOOD MANUFACTURING PRACTICES FOR ACTIVE SUBSTANCES OF THE WORLD HEALTH ORGANISATION (WHO) – FORTY-FOURTH TECHNICAL REPORT, NO. 957, 2010, ANNEX 2. ARE THESE STANDARDS EQUIVALENT TO THOSE IN THE EU, AS REQUIRED ACCORDING TO EU LEGISLATION?
Answer: Yes.

8. QUESTION: IN MY NON-EU COUNTRY, THE APPLICABLE STANDARDS ARE ICH Q7. ARE THESE STANDARDS EQUIVALENT TO THOSE IN THE EU, AS REQUIRED

ACCORDING TO EU LEGISLATION?
Answer: Yes.

9. QUESTION: DOES THE WRITTEN CONFIRMATION HAVE TO BE ISSUED BY A CENTRAL, REGIONAL OR LOCAL AUTHORITY?
Answer: Each non-EU country decides autonomously which body within that country issues the written confirmation. That non-EU country may decide to issue the written confirmation at central, regional or local level.

10. QUESTION: DO THE RULES APPLY ALSO TO ACTIVE SUBSTANCES CONTAINED IN AN IMPORTED FINISHED MEDICINAL PRODUCT?
Answer: No. Regarding finished medicinal products, the rules for importation of finished medicinal products (importation authorisation and batch release by a qualified person, see Articles 40(3) and 51 of Directive 2001/83/EC) apply. These rules remain unchanged.

10A: QUESTION: IS WRITTEN CONFIRMATION ALSO REQUIRED FOR A STARTING MATERIAL OR AN INTERMEDIATE USED FOR THE PRODUCTION OF AN ACTIVE SUBSTANCE, FOR EXAMPLE BY WAY OF PURIFICATION OR FURTHER SYNTHESIS?
Answer: No. Such starting material or intermediate used for the production of an active substance does not fulfil the definition of Article 1(3a) of Directive 2001/83/EC.

11. QUESTION: IS THE WRITTEN CONFIRMATION ALSO REQUIRED FOR IMPORTED ACTIVE SUBSTANCES WHICH HAVE ALREADY BEEN MIXED WITH EXCIPIENTS, WITHOUT YET BEING THE FINISHED MEDICINAL PRODUCT?
Answer: No. Such partial manufacturing of the finished product is not included in the rules on the written confirmation.

11A. QUESTION: IS THE WRITTEN CONFIRMATION ALSO REQUIRED WHERE THE FINISHED DOSAGE FORM MANUFACTURED IN THE EU IS DESTINED FOR EXPORTATION ONLY?
Answer: Yes.

12. QUESTION: WHO CHECKS THAT THE IMPORTED ACTIVE SUBSTANCE IS ACCOMPANIED BY THE WRITTEN CONFIRMATION?
Answer: This should be checked by the receiving manufacturer of the finished medicinal product. It may also be checked by the importer of the active substance upon its importation.
The verification whether such checks take place depends on the transposing law of the Member State where the active substance is imported. It may be verified
- by the relevant authority upon importation; and/or
- in the context of an inspection of the importer of the active substance, and/or
- in the context of an inspection of the manufacturer of the medicinal product that uses the imported active substance.

13. QUESTION: HOW CAN I CHECK IF THE WRITTEN CONFIRMATION IS AUTHENTIC?
Answer: You should contact the manufacturer of the active substance or the issuing authority in the non-EU country.

14. QUESTION: IS THE WRITTEN CONFIRMATION SENT TO AN EU REGULATORY AGENCY?
Answer: No. The written confirmation accompanies the imported active substance.

15. QUESTION: DOES THE WRITTEN CONFIRMATION HAVE TO BE SUBMITTED WITH A REQUEST FOR AUTHORISATION OF A MARKETING AUTHORISATION OF A MEDICINAL PRODUCT?
Answer: No.

16. QUESTION: IS THE WRITTEN CONFIRMATION TO BE ISSUED FOR EACH BATCH/CONSIGNMENT'?
Answer: No. The written confirmation is issued per manufacturing plant and the active

substance(s) manufactured on this site.

17. QUESTION: DOES EACH IMPORTED CONSIGNMENT HAVE TO BE ACCOMPANIED BY THE WRITTEN CONFIRMATION?
Answer: Yes.

18. QUESTION: IS IT ACCEPTABLE THAT THE WRITTEN CONFIRMATION ACCOMPANYING THE IMPORTED CONSIGNMENT OF THE ACTIVE SUBSTANCE IS A COPY?
Answer: Yes, provided that the original written confirmation is still valid.

18A: QUESTION: REGARDING THE WRITTEN CONFIRMATION OF 'EQUIVALENT' STANDARDS OF GOOD MANUFACTURING PRACTICE, CAN THE ISSUING AUTHORITY OF THE NON-EU COUNTRY BASE ITSELF ON INSPECTION RESULTS FROM EU AUTHORITIES OR OTHER AUTHORITIES APPLYING EQUIVALENT STANDARDS FOR GOOD MANUFACTURING PRACTICE, SUCH AS US FDA?
Answer: Yes. In this case, the written confirmation should indicate which authority has inspected the site.

18B: QUESTION: REGARDING THE WRITTEN CONFIRMATION OF 'EQUIVALENT' STANDARDS OF GOOD MANUFACTURING PRACTICE, CAN THE ISSUING AUTHORITY OF THE NON-EU COUNTRY BASE ITSELF ON INSPECTIONS CONDUCTED IN THE PAST?
Answer: Yes. It is not necessary to conduct an inspection specifically for the purpose of issuing the 'written confirmation'.

19. QUESTION:WHAT IS THE VALIDITY PERIOD OF THE WRITTEN CONFIRMATION?
Answer: The validity of the written confirmation is established by the issuing authority of the non-EU country.

19A. THE WRITTEN CONFIRMATION REFERS TO 'UNANNOUNCED INSPECTIONS'. DOES THIS MEAN THAT AN UNANNOUNCED INSPECTION HAS TO HAVE BEEN CONDUCTED?
Answer: No. Rather, the system of supervision as a whole (including different types of inspections, such as unannounced inspections) has to ensure a protection of public health at least equivalent to that in the EU.

20. QUESTION: IF ACTIVE SUBSTANCES ARE MANUFACTURED IN A NON-EU COUNTRY 'A', BUT IMPORTED IN THE EU VIA THE NON-EU COUNTRY 'B', WHO HAS TO ISSUE THE WRITTEN CONFIRMATION?
Answer: The written confirmation accompanying the imported active substance has to be issued by the non-EU country where the active substance is manufactured (i.e. non-EU country 'A').

21. QUESTION: THE TEMPLATE FOR THE WRITTEN CONFIRMATION REFERS TO A 'CONFIRMATION NUMBER'. DOES THIS NUMBER HAVE TO BE A SEQUENTIAL NUMBER PER COUNTRY?
Answer: No. This number would be attributed by the issuing authority of the non-EU country.

22. QUESTION: THE TEMPLATE FOR THE WRITTEN CONFIRMATION REFERS TO A 'RESPONSIBLE PERSON' IN THE ISSUING AUTHORITY. DOES THIS RESPONSIBLE PERSON HAVE TO HAVE A SPECIFIC QUALIFICATION?
Answer: No. The 'responsible person' in this context is the person responsible within the administration for issuing the written confirmation.

23. QUESTION: ACCORDING TO THE TEMPLATE FOR THE WRITTEN CONFIRMATION, INFORMATION OF FINDINGS RELATING TO NON-COMPLIANCE ARE SUPPLIED TO THE EU. TO WHOM THIS INFORMATION SHOULD BE SENT TO?
Answer: The information should be sent to the European Medicines Agency (qdefect@ema.europa.eu).

24. QUESTION: IS THE WRITTEN CONFIRMATION ALSO REQUIRED WHERE THERE IS A 'MUTUAL RECOGNITION AGREEMENT' BETWEEN A NON-EU COUNTRY AND THE EU?
Answer: Yes. The process of a written confirmation is independent of the existence of 'mutual recognition agreements'.

25. QUESTION: IF A MANUFACTURING PLANT IS LOCATED IN A NON-EU COUNTRY 'A', CAN THE WRITTEN CONFIRMATION BE ISSUED BY AN AUTHORITY IN ANOTHER NON-EU COUNTRY (NON-EU COUNTRY 'B')?
Answer: No.

26. QUESTION: ARE THERE EXCEPTIONS FROM THE REQUIREMENT OF A WRITTEN CONFIRMATION?
Answer: The Commission publishes a list of countries which, following their request, have been assessed and are considered as having equivalent rules for good manufacturing practices to those in the EU. Active substances manufactured in these countries do not require a written confirmation.
See also Questions n° 27 and 28.

27. QUESTION: WHERE CAN I FIND THE LIST OF NON-EU COUNTRIES TO WHICH THE REQUIREMENT OF A WRITTEN CONFIRMATION DOES NOT APPLY?
Answer: The list is published in the *Official Journal of the European Union* and also reproduced here: http://ec.europa.eu/health/human-use/quality/index_en.htm.

28. QUESTION: HOW MANY NON-EU COUNTRIES HAVE SO FAR REQUESTED TO BE LISTED?
Answer: A list of non-EU countries which have so far requested to be listed is available here: http://ec.europa.eu/health/human-use/quality/index_en.htm.

29. QUESTION: WHEN IS THE LIST GOING TO BE PUBLISHED BY THE COMMISSION?
Answer: The Commission is going to publish an additional non-EU country on the list once its equivalence assessment has been finalised. The equivalence-assessment takes several months from the request from the non-EU country.

29A: QUESTION: HOW DOES A NON-EU COUNTRY REQUEST TO BE LISTED?
Answer: The request is made by way of a letter to the Director-General of DG SANTE. It should contain the relevant information for conducting the 'equivalence assessment'.
More information on the procedure and the documents to be submitted is available here: http://ec.europa.eu/health/human-use/quality/index_en.htm, under the section "Listing of third countries".
The relevant information can also be sent directly to the responsible service within the Commission (sante-pharmaceuticals-b4@ec.europa.eu).

30. QUESTION: DO I NEED A WRITTEN CONFIRMATION, EVEN THOUGH MY MANUFACTURING SITE HAS RECENTLY BEEN INSPECTED BY THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES (EDQM) OF THE COUNCIL OF EUROPE?
Answer: Yes. The process of a written confirmation is independent of such inspection activities. See also Question n° 31.

31. QUESTION: DO I NEED A WRITTEN CONFIRMATION, EVEN THOUGH MY MANUFACTURING SITE HAS RECENTLY BEEN INSPECTED BY AN EU MEMBER STATE?
Answer: Yes. The process of a written confirmation is independent of such inspection activities. However, exceptionally and where necessary to ensure the availability of medicinal products, following inspections by an EU Member State, a Member State may decide to waive the need for a written confirmation for a period not exceeding the validity of the GMP certificate ('waiver').

32. QUESTION: I WOULD LIKE TO BE INSPECTED BY AN EU MEMBER STATE.WHERE

DO I 'APPLY' FOR SUCH AN INSPECTION?
Answer: You should address through
- any registered importer of the active substance;
- any holder of a manufacturing authorisation that uses the active substance;
- any holder of a marketing authorisation that lists the active substance manufacturer

to the national competent authority of the EU Member State where they are established.

33. QUESTION:WHAT HAPPENS WHEN AN ACTIVE SUBSTANCE MANUFACTURING SITE COVERED BY A WRITTEN CONFIRMATION IS FOUND GMP NON-COMPLIANT FOLLOWING AN INSPECTION BY AN EU MEMBER STATE?
Answer: A statement of GMP non-compliance issued by a EU Member State for a specific site and API supersedes the corresponding written confirmation until the noncompliance is resolved.

34. QUESTION: WHERE CAN I FIND A LIST OF ACTIVE SUBSTANCE MANUFACTURING SITES THAT RECEIVED STATEMENTS OF GMP NON-COMPLIANCE?
Answer: Statements of GMP non-compliance are stored in the EudraGMDP database (http://eudragmdp.eudra.org/inspections/displayWelcome.do) and publicly available.

35. QUESTION: CAN AN API BATCH MANUFACTURED DURING THE PERIOD OF VALIDITY OF A WRITTEN CONFIRMATION BE IMPORTED INTO THE EU ONCE THE WRITTEN CONFIRMATION IS EXPIRED?
Answer: Article 46(b)(2)(b) sets out that active substances can only be imported if manufactured in accordance with EU GMP or equivalent, and accompanied by a written confirmation from the competent authority of the exporting third country certifying, inter alia, that (1) the GMP standards applicable to the manufacturing plant are equivalent to those of the EU, and (2) the supervision of the plant compliance with GMP ensures a protection of public health equivalent to that of the EU.

It is legitimate to consider that the guarantees of equivalence provided by the written confirmation apply to any API batch in the scope of the written confirmation which was released for sale within the period of validity of the written confirmation, even if not exported in that time period.

Against this background, it can therefore be considered that the importation into the EU of an API accompanied by an expired WC is acceptable provided that the paperwork accompanying the consignment (1) unequivocally proves that the whole consignment has been manufactured and released for sale by the quality unit before the expiry date of the written confirmation; and (2) provides a solid justification of why a valid written confirmation is not available.

3. MHRA (UK) – Questions and Answers on GMP for Investigational Medicinal Products

Manufacture / Reconstitution

1. *My investigational medicinal product (IMP) unit is engaged in reconstituting sterile injections and then giving them to the clinical trial subjects. What licence, if any, do I need?*

A simple reconstitution or dilution (including serial dilution) of an IMP including a sterile injection for the purpose of administration falls outside the definition of manufacture and so no Manufacturer's Authorisation for Investigational Medicinal Products (MIA(IMP)) would be needed. It is also permissible without an MIA(IMP) to label them after reconstitution with an identifier to ensure that the dose goes to the correct subject. See also Q23 for further information.

1a. The reconstitution we are carrying out involves the addition of another material as well as the diluent. Does this still fall outside the definition of manufacture?

This may fall within the scope of manufacture; however it depends upon the nature of and reasons for multiple additions. Any operation such as weighing out, adding other materials, or combining IMPs is not considered to be for the purposes of administration and so would require appropriate authorisation under a MIA(IMP). This situation is potentially complicated and should be considered on a case-by-case basis by the MHRA. Ideally this should be discussed with a MHRA Clinical Trials pharmaceutical assessor pre-submission.

Licensing and Testing

2. *I know that small quantities of medicinal products can be manufactured and labelled by my local hospital with no licence at all as long as it is done by a pharmacist. Why is a hospital required to hold an MIA(IMP) authorisation to conduct a similar activity for IMPs?*

The Human Medicines Regulations 2012 applies to therapeutic doses. In this legislation there are some exemptions from the need for a manufacturing licence such as the 'Section 10' exemption which can be invoked here. There is no such exemption for the manufacture of IMPs. So, the manufacture of even one dose for immediate use requires an MIA(IMP) authorisation and Qualified Person (QP) certification.

2a. Does this mean that all such manufactured IMPs need to be analytically tested before they can be certified, even if the quantity is very small?

Yes. The analytical requirements should be agreed with MHRA Clinical Trials via the clinical trial application (CTA). If an activity defined as manufacture takes place (see above) then the resultant IMPs should be tested to confirm that the specification submitted in the CTA is met. There may be exceptions for certain types of products, e.g. ATIMPs or radiolabelled IMPs where testing may not be performed prior to release due to very short shelf life, however the associated rationale should be documented and agreed by MHRA Clinical Trials in advance.

2b. Does the release testing for my IMP need to be carried out in a GMP-certified laboratory?

It would be expected that the analysis would be performed in a GMP-compliant laboratory. Testing in support of certification and release is considered part of manufacturing and therefore compliance with GMP is expected. For an IMP, the certifying QP may rely on the results of analysis from a non-EU laboratory and not repeat testing on import to the EU/UK, however they must assure themselves that the laboratory is compliant with EU GMP as part of the process of supply chain assurance and issuance of the QP Declaration for import. This is described in the sections relating to release of batches within EU GMP Annex 13.

3. *Please clarify reference sample requirements for IMPs*

Paragraph 8 in Part 2, Schedule 7 of the Medicines for Human Use (Clinical Trials) Regulation 2004 (as amended) [SI 2004 1031] requires the manufacturing authorisation holder to keep samples of each batch of formulated products readily available for examination. There should be enough finished packs for testing in

duplicate. As IMPs are often small packing runs from one bulk batch, EU GMP Annex 19 accepts a justification for retaining the required sample quantity of the bulk batch and separate samples of packaging components used on each packing run. The sample of the bulk batch should be in the final primary pack in order to be representative of the materials supplied for use on a clinical trial. The requirements are also detailed in EU GMP Annex 13.

Samples of IMPs used in UK clinical trials should be stored within the UK, EEA or an MRA country unless suitably justified and defined in a technical agreement between the sponsor, importer and third country manufacturer (cost of the IMP itself would not be considered an acceptable justification to not hold appropriate samples).

4. ***We have a contract to supply the local hospital with 'Specials' and IMPs. We are even located within a hospital site. We need to employ a QP at great expense just to certify the IMPs. We have never needed one for the specials. Why?***

'Specials' are unlicensed medicines which are manufactured under a manufacturer's specials licence (MS) for a special clinical need and are under the responsibility of the prescribing doctor. There is no requirement for QP certification of products manufactured under the provisions of an MS. IMPs are governed by different legislation (The Medicines for Human Use (Clinical Trials) Regulation 2004 (as amended) [SI 2004 1031]). IMPs are not 'Specials'. A clinical trial authorisation application including a description of the IMPs has to have been submitted to the MHRA. A QP certification against that clinical trial authorisation is required for each batch of IMP.

5. ***I work in a clinical trials unit situated in my local hospital. We have an MIA(IMP) and carry out assembly of IMPs for immediate use within the unit. However, the hospital production unit itself assembles IMPs and doesn't have a MIA(IMP). Is this permissible?***

Regulation 37 of The Medicines for Human Use (Clinical Trials) Regulation 2004 (as amended) [SI 2004 1031] contains a specific exemption which is relevant here. This provides an exemption from the need for a hospital or health centre (both are defined in Regulation 2 of the Clinical Trials Regulations) to hold a MIA(IMP) authorisation to assemble an IMP in a hospital or health centre, when the 'assembly' is carried out by a doctor or pharmacist, or under the supervision of a pharmacist. 'Assembly' is related to packaging and labelling only and not to the preparation of medicines from their ingredients. The exemption applies only if the product is to be used exclusively in that hospital or health centre or any other that is a trial site for the same clinical trial in which the product is to be used. This exemption does not apply to anyone else such as separate organisations which happen to be situated within a hospital or to companies which have a contract to supply hospitals or health centres.

6. ***We perform over encapsulation of tablets in order to blind them. Capsules are containers so this counts as packaging doesn't it?***

No. Capsules are specifically excluded from the definition of a container in the Clinical Trials Regulations SI 2004 1031. An MIA(IMP) with 'capsule manufacture' listed as authorised would be necessary in this case.

7. ***We are a firm of respected pharmaceutical consultants some of whom are QPs. We do a lot of contract regulatory and auditing work for companies involved in clinical trials and the manufacture of IMPs. Can we have a MIA(IMP) so that we can perform IMP certification for our clients?***

No. An organisation cannot act as a contract batch certification site only. The sponsors of a clinical trial may wish to keep the final QP certification step of IMP manufacture in house as they carry ultimate responsibility for the trial. Otherwise, any contract organisation such as yours must be involved with some manufacturing or importation of an IMP if they wish to carry out batch certification.

8. ***We wish to enter the business of storing and distributing IMPs. What licences do we need if any?***

There is no requirement within the legislation for any MHRA licence to carry out storage and distribution of IMPs. In this respect, the legislation differs from that for medicinal products. However, you will need to be

named within the appropriate annex of your client's MIA(IMP) as a site of storage and distribution. Therefore, any clients who wish to make use of your services will need to vary their MIA(IMP) accordingly.

Note that the storage and distribution of a licensed medicinal product must remain in the licensed distribution chain until it is supplied to the Sponsor for use in a trial.

9. ***We prepare radio-imaging pharmaceuticals from licenced kits and Technetium generators for use in clinical trials. Do we need an MIA(IMP)?***

The preparation of such radiopharmaceuticals using Technetium generators is considered to be manufacture and so an MIA(IMP) would be required if they were to be used as IMPs. Note that the Clinical Trial Regulations define an investigational medicinal product (including a licenced medicinal product) as being:

(a) used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation

(b) used for an indication not included in the summary of product characteristics under the authorization for that product

(c) used to gain further information about the form of that product as authorised under the authorization (Article 2).

Note: The UK CT Legislation is currently under review. Any changes to this position will be updated as necessary.

However, it may be that the radiopharmaceutical used in a clinical trial may not be an IMP. There are classes of products used in clinical trials which are 'not IMPs' (NIMPs) and details of the definitions can be found in Eudralex Volume 10 on Clinical Trials. NIMPs include challenge agents, rescue medication, agents used to assess end points and others. Clinical trial legislation does not apply to these as long as a), b) and c) don't apply.

Further information relating to NIMPs is included in Q18 and Q25.

10. ***We manufacture tablets used for IMPs and some of these contain penicillins or other beta-lactams. Does the MHRA need to know about such manufacture?***

Yes. The MHRA does need to know about such manufacture which brings with it special GMP considerations (the manufacture of doses containing potent Active Pharmaceutical Ingredients (APIs) would be another example). Please include the relevant information in the application form describing such manufacture.

In addition, details of the active materials / product types handled within your facility are requested as part of the pre-inspection compliance report and cross-contamination prevention is a focus of inspections following the revisions to EU GMP chapters 3 and 5.

11. ***We manufacture IMPs purely for export to countries outside the EEA. Do we need an MIA(IMP)?***

Yes. An MIA(IMP) licence is required for the manufacture of an IMP regardless of whether the IMP is for use in the UK, an EEA Member State or a non-EEA Member State (Third Country).

12. ***What is the regulatory situation with respect to veterinary clinical trials and IMPs?***

The Veterinary Medicines Directorate is responsible for such regulatory issues and contact details are available on the following link: https://www.gov.uk/government/organisations/veterinary-medicines-directorate.

13. ***What happens if there is an adverse event during a clinical trial and the possibility of a recall or product defect of IMPs?***

You should inform the Defective Medicines Report Centre (DMRC) at the MHRA as you would for a licensed or unlicensed medicinal product. It will also be necessary to inform the MHRA Clinical Trials at the MHRA. The Clinical Trial Regulations make provision for notification of adverse events and notification of suspected unexpected serious adverse reactions. Further guidance for handling investigations into possible product defects and product recall actions is detailed in Chapter 8 of the EU GMP Guide (Eudralex Vol 4).

Import

14. ***What sites should appear on the QP declarations relating to IMP manufacture in third countries which accompany CT applications?***

All sites involved in manufacturing steps starting with the conversion of the API into the dosage form and including primary and secondary packing and also any contract laboratories involved with release or stability testing. A guidance template for the information that should be included on the QP Declaration is provided in Eudralex Vol 10 Chapter III.

Note: Import of finished IMPs that have been QP certified in an EEA country into Great Britain requires an oversight process under the supervision of a UK MIA(IMP) holder (see Q15b), however this does not require a UK QP Declaration.

15. ***We need to import some IMPs from a manufacturing site in the USA. The site has had an inspection by an EU Competent Authority a few months ago. Does this mean that I don't need to go out there to do another audit myself before I sign the QP Declaration of GMP compliance?***

No. The starting point for a QP declaration of EU GMP should be an audit conducted by or on behalf of the importing company. Any departure from this should be justified and documented and will be subject to scrutiny during an MHRA inspection. It may be possible to use the fact of a regulatory inspection by an EU Competent Authority as part of this justification, but these are general inspections which may not address the specific technical or GMP issues associated with your product. It may not even have covered the same factory or part of the factory. A regulatory inspection cannot be used unconditionally to remove the need for your own audit. The audit does not need to be done by the QP, however the QP needs to be satisfied that it has been done correctly by an appropriately trained individual as the QP will be taking final responsibility.

15a. We also intend to use some IMPs that were manufactured at a site in Switzerland. Do we need to include a QP import declaration with the CTA submission? This will have been certified by a Swiss Responsible Person (RP) so does this also require certification by an EU QP?

Although there is a Mutual Recognition Agreement (MRA) with Switzerland, it remains a third country therefore the IMP would need to be imported by an MIA(IMP) holder. As such, a QP Declaration of EU GMP compliance would need to be included as part of the CTA for each site outside the EU and the IMP would need to be certified by a QP upon import prior to release for use in the clinical trial.

15b. We intend to use some IMPs for our trial in Great Britain that were manufactured at a site in the EU/EEA. Do we need to include a QP import declaration with the CTA submission? This will have been certified by an EEA QP so does this also require certification by a UK QP?

Since the UK's exit from the EU, and from January 2022, import of finished IMPs into Great Britain from EEA countries requires oversight by a UK MIA(IMP) holder. Additional certification by a UK QP is not required, however the UK MIA(IMP) holder responsible for the import oversight process needs to be listed in the UK CTA along with the site of final certification in the EEA.

The import oversight activity needs to be specifically authorised in the UK MIA(IMP) and an application or variation to an existing licence should be submitted and approved prior to undertaking this activity.

Further details on the requirements for this process can be found at the following link: https://www.gov.uk/government/publications/importing-investigational-medicinal-products-into-great-britain-from-approved-countries.

16. ***We import an IMP for a clinical trial which has just been halted for ethical reasons. We need to continue to supply the IMP as a therapy to patients who were on the trial. What is the regulatory situation here?***

Once a trial has stopped, the product ceases to be an IMP and becomes a medicinal product. If it is a licenced medicinal product then it can be purchased and supplied as normal from the authorised supply chain. However, more often than not, the ex-IMP will not be licenced.

Material already existing physically as an IMP in the UK can be retrospectively notified to the MHRA Import Notification System (INS) as an importation of unlicensed medicines according to MHRA Guidance Note 14. This regularises the stock as an unlicensed medicine and the packs can be supplied as such, should MHRA not object to it. The clinical trial particulars should be removed from the product particulars (labelling and product information) ahead of supply taking place. Any stock not currently in the UK must be notified to INS ahead of the importation taking place.

The importer of an unlicensed medicinal product (a "special") into the UK must hold; (a) a Wholesale Dealer's Licence (WDA (H)) if the product is to be imported from an EEA member state i.e. the EU plus Norway, Iceland and Liechtenstein, or (b) a Manufacturer's "Specials" Licence if the product is to be imported from a third country i.e. a non-EEA country.

The holder of the Wholesale Dealer's Licence or Manufacturer's "Specials" Licence, must comply with certain obligations in relation to the import of an unlicensed medicinal product, which are set out in Schedule 4 of the Human Medicines Regulations 2012. These are explained and summarised in MHRA Guidance note 14.

17. ***Are QP statements required for APIs used in IMPs?***

There is no requirement for APIs used in IMPs to comply with EU GMP Part II in full, but there remains a responsibility for IMP manufacturers to assure themselves that the API is of an appropriate quality. Section 19 of Part II of the GMP Guide describes the expectations. The EMA has also published a Q&A concerning the GMP status of APIs used in IMPs.

However, for Biological Products and Advanced Therapy Investigational Medicinal Products (ATIMP), there is a requirement for EU GMP Part I / Part IV to apply across all manufacturing steps as applicable, including from cell banks and vectors onwards, as detailed in EU GMP Annex 2 and in the PIC/S GMP Guide Annex 2A for manufacture of ATMPs for Human use for example. This is due to the ways in which Biological and Advanced Therapy medicinal products are manufactured and controlled, and the greater significance of the first steps in the manufacture of these products. As such all sites in third countries should be listed in the associated QP declaration for import as part of the submission for UK CTAs.

18. ***What is the regulatory situation for the importation of NIMPs into the UK?***

As such products are not IMPs, then the general requirements relating to medicinal products come into force, in particular the need for a Marketing Authorisation under the Human Medicines Regulations 2012. Where a medicinal product is not the subject of a valid Marketing Authorisation, the process for the supply of an unlicensed product provides a means of actually getting the NIMP into the UK for use in a clinical trial. The framework described in Guidance Note 14 is seen as an appropriate means of giving the legal method for the sponsor to actually obtain the NIMP, otherwise there would be no legal basis for supply. Further information on the importation of unlicensed medicines is available on the MHRA website: Supply of unlicensed medicinal products.

Stability / Shelf Life

19. ***We have got some more stability information on our IMP and wish to extend the shelf life. What do we do?***

Firstly, MHRA Clinical Trials would need to be informed via a variation to the CTA. Extension of shelf life represents a substantial amendment, unless you have previous agreement within the approved IMP Dossier to extend the shelf life when more stability information becomes available.

Secondly, the Product Specification File (PSF) would need to undergo a controlled change such that manufacturing sites and the QPs can take appropriate action such as updating labelling instructions, certification criteria etc.

Thirdly, if advantage of the longer shelf life is to be taken for IMPs already manufactured, these IMPs will need to be relabelled. This relabelling will need to be conducted, checked and documented in accordance with EU GMP Annex 13 (see also the following question).

20. ***Some of our stock has already gone out. Do we need to bring it back to the site with the MIA(IMP) to be relabelled with the new shelf life?***

No. Although this would be preferable, it is recognised that this shipping backwards and forwards could cause more GMP problems than it solves. It is permissible in these circumstances for the relabelling to be done at the clinical site. The certifying QP should certainly be aware of this and be involved in setting up the required GMP systems. The relabelling should be done by appropriately trained staff, documented, and the records stored in the original trial file. Any stock not already supplied to clinical sites should be relabelled prior to shipping.

Note that the EU GMP Annex 13 deals specifically with this issue. It states:

"If it becomes necessary to change the expiry date, an additional label should be affixed to the investigational medicinal product. This additional label should state the new expiry date and repeat the batch number and clinical trial reference number. It may be superimposed on the old expiry date, but, for quality control reasons, not on the original batch number.

The re-labelling operation should be performed by appropriately trained staff in accordance with good manufacturing practice principles and specific standard operating procedures and should be checked by a second person. This additional labelling should be properly documented in the batch records. To avoid mistakes the additional labelling activity should be carried out in an area that is partitioned or separated from other activities. A line clearance at the start and end of activity should be carried out and label reconciliation performed. Any discrepancies observed during reconciliation should be investigated and accounted for before release.

The re-labelling operation may be performed by authorised personnel at a hospital, health centre or clinic."

1. *a.* ***We have the stability data and necessary regulatory approval to extend the shelf life of our product and fully intend to include this new date for the next campaign of product. We have some remaining stock from a batch of IMP that we would like to continue to use in the ongoing trial however it is frozen material and therefore difficult to perform the relabelling activities. Can we continue to use the product past the labelled expiry date as long as we have the relevant information available to clinic staff?***

This approach is usually not acceptable, as this is not compliant with EU GMP or Annex 13 requirements, except where provision of IMP is critical to the ongoing care of trial participants and has been agreed by MHRA Clinical Trials in advance of implementation. It is expected that relabelling processes should be fully explored before seeking approval to bypass relabelling activities. It is likely that additional mechanisms will be required to manage the continued use of incorrectly labelled products whilst correctly labelled stock is made available. Any additional handling or cumulative time out of storage for the relabelling should also be considered in line with the available stability data and this should be appropriately documented within the associated records.

21. *If an IMP has a shelf life extension after QP certification and is consequently relabelled with a revised expiry date, is a further QP certification required?*

A new certification after relabelling is required for stock which has not been shipped to an investigator site. For product held at the trial site, QP certification is not required if the relabelling activity is carried out by, or under the supervision of a pharmacist, or other healthcare professional, with appropriate documented evidence in accordance with EU GMP Annex 13.

QPs and Packaging / Labelling Activities

22. *Do the MHRA issue certificates of eligibility for transitional IMP QPs?*

Confirmation that a transitional IMP QPs has been assessed as being suitable and eligible to act as a QP at a given site can be verified by referring to list of authorised personnel within the appropriate UK MIA(IMP) licence. Eligibility certificates for transitional IMP QPs were not issued by MHRA, however if a TQP has been previously named on a UK MIA(IMP) they will continue to be recognised as eligible in this capacity. On receipt of an application to name a TQP on an MIA(IMP), the individual's suitability will be assessed based on experience of both the authorised dosage forms and the company's systems.

Where an application to name a TQP on an MIA(IMP) is received, it is expected that this only applies to those already named on a previous MIA(IMP) licences. Any QP not yet known to the MHRA via inclusion on an MIA(IMP) will be expected to have undergone the applicable assessment via the Joint Professional Bodies on behalf of the MHRA.

The MHRA are no longer reassessing TQPs in line with the requirements of the EU Clinical Trials Regulation 536/2014 following the UK exit from the EU. This is a change from the approach indicated prior to leaving the EU.

23. *Annex 13 of the Orange Guide allows for some packaging and labelling to take place after QP certification, for example expiry updating at a trial site under the supervision of the clinical trial pharmacist. Under what circumstances is this permissible and what are the GMP expectations?*

This 'post certification labelling' can be used for the following and is expected to be performed prior to despatch in the distribution area at the MIA(IMP) holder site; or where justified and controlled then immediately prior to administration to a subject or patient:

- application of an identifier to ensure that a reconstituted IMP in its final container is administered to the correct subject
- application of expiry date labelling (or revised expiry date labelling) (see also Q20)
- application of an investigator name
- application of a protocol number.

It should, in the first instance, be done at a site with an MIA(IMP) unless the risk to the quality of the product is unacceptably elevated by any required transportation back to this site. The level of assurance of product quality should not be less than if this labelling were performed prior to QP certification. It should also be noted that there is no expectation for hospital pharmacy or investigator sites involved in the application of labels as part of the final dispensing process to return packs to a licensed facility for this process.

NOTE: Such labelling should not effectively incorporate allocation of doses against a randomisation code. It is important that allocation takes place before this to ensure adequate QA scrutiny and QP confirmation and to ensure that staff applying such post certification labels are not accidentally unblinded.

GMP expectations for 'post certification labelling' are:

- finished IMP doses, certified by a QP, should exist prior to the labelling
- the activity should be planned and described in the CT protocol
- relative responsibilities should be described in a technical agreement where appropriate
- the process should be described in an SOP

- personnel doing the labelling should be appropriately trained and retrained at intervals
- labels should be stored securely with arrangements in place to ensure that records for removal and usage are kept. Labels should be transported in a secure way from the label store to the location for use
- the activity should be carried out in an area which is partitioned or separated from other activities. It should also preferably be done in a quieter environment
- a line clearance at the start and end of the activity should be carried out and label reconciliation performed to 100%. An investigation should be carried out if this is not the case. This should be verified by a second person
- the activity should be recorded in a batch record or equivalent document which is subject to independent review
- the certifying QP should be aware of the post certification process and be satisfied that the elements described above are in place. Although further QP certification is not necessary, some oversight is expected, and some assurance should be gained (e.g. by sampling of records) to confirm that the process is being carried out correctly. If conducted at an investigator site the sponsor is responsible for ensuring that the activity is carried out in accordance with GMP, and the advice of the QP should be sought in this regard.
- the process should be covered by normal quality system elements such as change control and non-conformance management.

24. *What is the MHRA view on medication pooling?*

Medication pooling is the production of IMPs which may be used in a number of clinical trials and which are left in a "generic" state until after QP certification. This would usually be by leaving a space for the protocol number to be added at the point of dispensing, or where multiple protocol numbers are on the label with the others being deleted at the point of dispensing. Only after certification is it decided which protocol the particular IMPs are destined for, this is when it is being dispensed to the patient. This is acceptable provided that the QP certification is against all of the possible clinical trials which may use the IMP, the protocol number is added to the IMP doses prior to release to the trial, and the GMP points outlined in Q23 (above) are considered.

25. *What is the expectation for QPs in relation to non-investigational medicinal products?*

Non investigational medicinal products (NIMPs) are not IMPs and so the legislative requirements of The Medicines for Human Use (Clinical Trials) Regulation 2004 (as amended) [SI 2004/1031] (as amended) do not apply to such products. There is therefore no requirement to source such products from a site holding an MIA(IMP) or for QP certification of the product. There is an expectation for the Sponsor to ensure that NIMPs are of the necessary quality for human use. Further guidance on sourcing NIMPs is included in Eudralex Volume 10 Clinical Trials Notice to Applicants.

26. *Provided it is considered that the safety, quality and efficacy of a batch of IMP have not been compromised, does a QP have any discretion to certify that batch as suitable for release even if it does not meet the specification in the Clinical Trials Authorisation?*

As for licensed products, there is no such discretion available to a certifying QP. However, if a batch is manufactured and does not meet the authorised specification then a substantial amendment to alter the specification may be submitted to MHRA Clinical Trials provided it is deemed that safety, quality and efficacy are not compromised. If required, an expedited review may be requested via the Clinical Trials Helpline.

Administration of an Out of Specification (OOS) ATIMP may be acceptable in exceptional circumstances without or prior to a Substantial Amendment; however, these must be discussed with MHRA Clinical Trials with regards to impact to the trial prior to administration.

4. FDA (USA) – Questions and Answers on cGMP Requirements

General Provisions

1. Are USP general chapters above <999> considered equivalent to FDA guidance? What is their purpose and how should manufacturers use these informational chapters?

No, FDA is the only source of policy on pharmaceutical CGMP and quality. CGMP requirements are found in statutes and regulations, and FDA's current thinking on these requirements is explained in the Agency's guidance documents.

The U.S. Pharmacopeial Convention is a private, nongovernmental organization that publishes the United States Pharmacopeia (USP) and the National Formulary (NF) as official compendia of the United States. Although much of the USP and NF is legally enforceable, the USP general chapters numbered above <999> (general information chapters) are informational and generally do not contain any mandatory requirements (see USP General Notices 2.10). General information chapters might include some recommendations that may help a firm meet CGMP requirements.

2. How does one comment on FDA's proposed guidance documents? How about USP proposals?

Both USP and FDA have mechanisms in place for interested parties to make comments on proposed documents.

Guidance Documents
FDA's proposed guidance documents are written using good guidance practices and published for comment per 21 CFR 10.115. They are easily accessible to the public via our Web site and through the *Federal Register*. FDA's Division of Dockets Management is the office responsible for receiving all comments on proposed guidance. Interested parties can read and submit comments via FDA's Dockets Management Web site. FDA reviews all received public comments, makes appropriate modifications, and publishes a final document.

USP Monographs
USP publishes proposed chapters or monographs in the *Pharmacopeial Forum*, a publication that is issued bimonthly. USP subscribers have access to these publications and can send comments (within a 90-day post publication comment period) for consideration by the USP. Finalized proposals (official revisions, new chapters, or monographs) are published in subsequent supplements to or editions of the Pharmacopeia.

Buildings and Facilities

1. What is penicillin?

Penicillin is defined as a group of natural or semi-synthetic antibiotics derived from fungi strains of the genus *Penicillium*. Generally, all penicillins share a three-carbon, one-nitrogen, and four-member cyclic amide structure, known as the beta-lactam ring.

Reference:

- Lewis, J, and K Bush, 2015, Antibacterial Agents, In: J Jorgensen, M Pfaller, K Carroll, G Funke, M Landry, S Richter, D Warnock, eds. Manual of Clinical Microbiology, 11th ed., Washington, DC: ASM Press, 1171-1211.

Date: 6/29/2009

2. What are the penicillin drugs?

The Manual of Clinical Microbiology, 11th edition, identifies penicillin drugs as follows:

Natural

- Benzylpenicillin (penicillin G)*
- Phenoxymethyl penicillin (penicillin V)*

Semisynthetic

Penicillinase resistant:

- Cloxacillin*
- Dicloxacillin*
- Nafcillin
- Oxacillin
- Temocillin**

Extended spectrum:

- Aminopenicillins
  - Amoxicillin*
  - Ampicillin*
  - Mecillinam**
- Carboxypenicillin
  - Ticarcillin*
- Ureidopenicillin
  - Piperacillin

*Approved for veterinary use
**Not approved in the United States

Please be aware that penicillin trade names may vary by region and country. Manufacturers, including repackers, are responsible for knowing whether their drug is penicillin. FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) or Drugs@FDA, both of which are located on FDA's Web site, enable searching by trade name (i.e., proprietary name) and by active ingredient name (i.e., generic or non-proprietary name).

References:

- Lewis, J, and K Bush, 2015, Antibacterial Agents, In: J Jorgensen, M Pfaller, K Carroll, G Funke, M Landry, S Richter, D Warnock, eds. Manual of Clinical Microbiology, 11th ed., Washington, DC: ASM Press, 1171-1211.
- FDA Orange Book
- Drugs@FDA

Date: 6/29/2009

3. Is cross-contamination a concern with penicillin drugs?

Yes, penicillin can be a sensitizing agent that triggers a hypersensitive exaggerated allergic immune response in some people. Differences in the chemically substituted 6-aminopenicillanic acid side chain can generate allergic reactions ranging from skin rashes to life-threatening anaphylaxis.

Reference:

- Lewis, J, and K Bush, 2015, Antibacterial Agents, In: J Jorgensen, M Pfaller, K Carroll, G Funke, M Landry, S Richter, D Warnock, eds. Manual of Clinical Microbiology, 11th ed., Washington, DC: ASM Press, 1171-1211.

Date: 6/29/2009

4. Are there special manufacturing requirements for penicillin drugs?

Yes, all penicillin finished pharmaceutical manufacturers, including repackers, are required by the CGMP regulations to establish a comprehensive control strategy designed to prevent cross-contamination of other drugs with penicillin. These requirements include:

- 21 CFR 211.42(d): Separation of facility and equipment
- 21 CFR 211.46(d): Separate air handling systems (HVAC)
- 21 CFR 211.176: Test for traces of penicillin where possible exposure exists.

Penicillin active pharmaceutical ingredients (APIs) are also required to be manufactured under CGMP in accordance with section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. FDA has published internationally harmonized guidance on the manufacture of APIs; see ICH guidance for industry, *Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*. Chapter 4, section 4.4 of this guidance describes actions API manufacturers, including those that manufacture or package APIs or penicillin intermediates, should follow to ensure such material is contained and does not contaminate other drugs.

References:

- FDA CGMP regulations (21 CFR parts 210–211)
- Federal Food, Drug, and Cosmetic Act, section 501(a)(2)(B)
- FDA Guidance for Industry, 2001, ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

Date: 6/29/2009

5. Why is FDA concerned about drug contamination with halogenated anisole compounds, such as 2,4,6-tribromoanisole (TBA)?

Reports, including some dating back several decades, describe a moldy or musty odor in food (and wine) products due to contamination with trace amounts of halogenated anisole compounds such as 2,4,6-tribromoanisole (TBA). An odor attributable to the presence of a halogenated anisole compound can be detected by consumers even when the offending compound is present at parts per billion or lesser levels. An upward trend in consumer complaints about musty or moldy odor led a drug firm to identify TBA as the odor-causing compound. The firm's investigation of this incident led to the detection of TBA in several oral products. The firm traced all of the contamination back to the use of certain wooden pallets used to transport drug packaging materials. TBA is prone to volatilize and adsorb onto articles stored near the TBA source. Because of their volatility, it appears that even minute levels of halogenated anisole compounds can adversely affect a large quantity of product in a single contamination incident.

Date: 3/12/2010

6. Are there any health effects associated with ingestion of halogenated anisole compounds?

Although there is no meaningful toxicological data on TBA at these levels, the health risks appear to be minimal. Currently available data indicate that serious adverse health effects have not resulted from ingestion of drugs or foods contaminated with halogenated anisole compounds at the levels of contamination that have been reported. However, there are some reports of gastrointestinal events by consumers who also report sensing a foul odor, or taste, in drug products contaminated with the typical trace levels of TBA. Even if the health effects are minimal, FDA is concerned that patients sensing an unusual odor that is not intrinsic to the product will stop taking their medication.

Date: 3/12/2010

7. Has FDA identified the source of the halogenated anisole compounds that have contaminated drug products?

The source of TBA-contaminated drug products appears to have been 2,4,6-tribromophenol (TBP), a chemical used as a wood preservative. Certain fungi are able to survive in TBP-treated wood by converting TBP to its anisole analog, TBA.[1] In the contamination incident, an investigation found that TBP-treated wood was used to manufacture pallets that were then used to ship and store drug packaging material. Currently, the use of halogenated phenolic compounds to preserve wood appears to be very rare as this practice is either

discouraged or prohibited in many regions of the world, including the United States. However, TBP treatment of wood continues in some regions that supply wood to the United States and other countries.

[1]Trichlorophenol (TCP) is another example of a compound that can be converted to a halogenated anisole compound.

Date: 3/12/2010

8. What is FDA's expectation for preventing contamination of drug products with halogenated anisole compounds?

FDA recommends that manufacturers and distributors take precautions to prevent the use of wood products treated with or exposed to a halogenated phenolic preservative anywhere in the supply chain. This includes all facilities that manufacture, hold, or distribute drug products, components, or packaging materials. We recommend that manufacturers not store drug products, components, or packaging materials near wood or wood-derived storage materials unless there is assurance that the wood material has not been treated with a halogenated phenolic preservative.
FDA further recommends that manufacturers establish agreements and request certification from suppliers to provide assurance that halogenated phenolic preservatives are not present. Manufacturers should also be vigilant to the characteristic odor of the offending compounds so they can intervene before products are contaminated or further distributed.

Date: 3/12/2010

9. Are there any standards applicable to preventing contamination of drug products with halogenated anisole compounds?

U.S. (ASTM) and international standards (International Standard for Phytosanitary Measures (ISPM)) recommend heat treatment, or fumigation with methyl bromide, for the preservation of wood-derived packaging storage materials, including wood pallets. For more information, including certification to these standards, refer to Standard Practice for Treatment and/or Marking of Wood Packaging Materials (ASTM D 6253-10) and Guidelines for Regulating Wood Packaging Material in International Trade (ISPM 15).

References:

- ASTM Standard D6253-10, 2010, Standard Practice for Treatment and/or Marking of Wood Packaging Materials, West Conshohocken, PA: ASTM InternationalExternal Link Disclaimer
- ISPM 15, 2013, Guidelines for Regulating Wood Packaging Material in International Trade, Rome: Secretariat of the International Plant Protection Convention of the Food and Agriculture Organization of the United NationsExternal Link Disclaimer

Date: 3/12/2010

10. Can contamination of drug products with halogenated anisole compounds be detected?

Although methods for detection exist and might be practical for periodic screening, FDA expects that manufacturers prevent such contamination through adherence to CGMP. A CGMP-compliant quality system will ensure that assurances are obtained from suppliers and that measures are taken to prevent exposure to problematic compounds. Manufacturers of finished pharmaceuticals are reminded that the CGMP regulations at 21 CFR 211.56(c) require written procedures for sanitation designed to prevent the contamination of equipment, components, drug product containers, closures, packaging, labeling materials, and drug products. Analogous recommendations for manufacturers of active pharmaceutical ingredients are included in internationally harmonized ICH guidance for industry *Q7 Good Manufacturing Guidance for Active Pharmaceutical Ingredients* (section 4.7).

References:

- 21 CFR 211.56: Sanitation
- FDA CGMP regulations (21 CFR parts 210–211)

- FDA Guidance for Industry, 2001, ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

Equipment

1. Many leading analytical balance manufacturers provide built-in "auto-calibration" features in their balances. Are such auto-calibration procedures acceptable instead of external performance checks? If not, then what should the schedule for calibration be?

The auto-calibration feature of a balance may not be relied upon to the exclusion of an external performance check (21 CFR 211.68). For a scale with a built-in auto-calibrator, we recommend that external performance checks be performed on a periodic basis, but less frequently as compared to a scale without this feature. The frequency of performance checks depends on the frequency of use of the scale and the criticality and tolerance of the process or analytical step. Note that all batches of a product manufactured between two successive verifications would be affected should the check of the auto-calibrator reveal a problem. Additionally, the calibration of an auto-calibrator should be periodically verified—a common frequency is once a year—using National Institute of Standards and Technology (NIST)-traceable standards or NIST-accredited standards in use in other countries.

References:

- 21 CFR 211.68: Automatic, mechanical, and electronic equipment
- 21 CFR 211.160(b)(4): General requirements (Laboratory Controls)
- United States Pharmacopeia (USP) General Chapter <41> Weights and Balances
- See also ASTM Standard E 617, 2013, Standard Specification for Laboratory Weights and Precision Mass Standards, West Conshohocken, PA: ASTM InternationalExternal Link Disclaimer (This standard is incorporated into the USP by reference; other widely recognized standards may be acceptable.)

Date: 8/4/2004

2. Is there a list of CDER-approved drug manufacturing equipment?

No. The CGMP regulations neither approve nor prohibit specific equipment for use in manufacturing of pharmaceutical products (with the exception of asbestos and fiber-releasing filters, see 21 CFR 211.72). We do not maintain a list of approved equipment. Firms are afforded the flexibility to select equipment that best satisfies their particular needs and that is capable of meeting the relevant CGMP requirements. Each firm is responsible for selecting all equipment used in their manufacturing process to produce quality products in accordance with CGMP. They are also responsible for selecting the appropriate intended use for the equipment's operation and are free to modify standard equipment designs to best suit their process and that are compatible with the product under process.

The CGMP regulations require that equipment be of appropriate design to facilitate operations for its intended use and for cleaning and maintenance (see 21 CFR 211.63 and 211.67) and, that any equipment surface in contact with components, in-process materials, or drug products not be reactive, additive, or absorptive so as to "alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements" (see 21 CFR 211.65).

References:

- 21 CFR 211.63: Equipment design, size, and location
- 21 CFR 211.65: Equipment construction
- 21 CFR 211.67: Equipment cleaning and maintenance
- 21 CFR 211.68: Automatic, mechanical, and electronic equipment
- 21 CFR 211.72: Filters

Date: 5/18/2005

3. Can Total Organic Carbon (TOC) be an acceptable method for detecting residues of contaminants in evaluating cleaning effectiveness?

Yes. Since the publication of the inspection guide on cleaning validation in 1993, a number of studies have been published to demonstrate the adequacy of TOC in measuring contaminant residues.

TOC or TC can be an acceptable method for monitoring residues routinely and for cleaning validation. In order for TOC to be functionally suitable, it should first be established that a substantial amount of the contaminating material(s) is organic and contains carbon that can be oxidized under TOC test conditions. This is an important exercise because some organic compounds cannot be reliably detected using TOC.

TOC use may be justified for direct surface sample testing as well as indirect (rinse water) sample testing. In either case, because TOC does not identify or distinguish among different compounds containing oxidizable carbon, any detected carbon is to be attributed to the target compound(s) for comparing with the established limit. Thus, a firm should limit background carbon (i.e., carbon from sources other than the contaminant being removed) as much as possible. The established limit, or the amount of residue detected for comparison to the specification, should correct for the target material's composition of carbon. As for any cleaning method, recovery studies are necessary (21 CFR 211.160(b)). If TOC samples are being held for long periods of time before analysis, a firm should verify the impact of sample holding time on accuracy and limit of quantitation.

References:

21 CFR 211.67: Equipment cleaning and maintenance
21 CFR 211.160(b): General requirements (Laboratory Controls)
USP General Chapter <643> Total Organic Carbon
FDA Guide to Inspections: Validation of Cleaning Processes
Date: 5/18/2005

4. A firm has multiple media fill failures. They conducted their media fills using TSB (tryptic soy broth) prepared by filtration through a 0.2 micron sterilizing filter. Investigation did not show any obvious causes. What could be the source of contamination?

A firm had multiple media fill failures. The media fill runs, simulating the filling process during production, were conducted inside an isolator. The firm used TSB (nonsterile bulk powder) from a commercial source and prepared the sterile solution by filtering through a 0.2 micron sterilizing filter. An investigation was launched to trace the source of contamination. The investigation was not successful in isolating or recovering the contaminating organism using conventional microbiological techniques, including the use of selective (e.g., blood agar) and nonselective (e.g., TSB and tryptic soy agar) media, and examination under a microscope. The contaminant was eventually identified to be *Acholeplasma laidlawii* by using 16S rRNA gene sequence. The firm subsequently conducted studies to confirm the presence of *Acholeplasma laidlawii* in the lot of TSB used. Therefore, it was not a contaminant from the process, but from the media source.

Acholeplasma laidlawii belongs to an order of *Mycoplasma*. *Mycoplasma* contain only a cell membrane and have no cell wall. They are not susceptible to beta-lactams and do not take up Gram stain. Individual organisms are pleomorphic (assume various shapes from cocci to rods to filaments), varying in size from 0.2 to 0.3 microns or smaller. It has been shown that *Acholeplasma laidlawii* is capable of penetrating a 0.2 micron filter, but is retained by a 0.1 micron filter (see Sundaram, Eisenhuth, et al. 1999). *Acholeplasma laidlawii* is known to be associated with animal-derived material, and microbiological media is often from animal sources. Environmental monitoring of *Mycoplasma* requires selective media (PPLO broth or agar).

Resolution:

For now, this firm has decided to filter prepared TSB, for use in media fills, through a 0.1 micron filter (note: we do not expect or require firms to routinely use 0.1 micron filters for media preparation). In the future, the firm will use sterile, irradiated TSB when it becomes available from a commercial supplier. (Firm's autoclave is too small to permit processing of TSB for media fills, so this was not a viable option.) The firm will continue monitoring for *Mycoplasma* and has revalidated their cleaning procedure to verify its removal. In this case, a thorough investigation by the firm led to a determination of the cause of the failure and an appropriate corrective action.

References:

- 21 CFR 211.113: Control of microbiological contamination
- 21 CFR 211.72: Filters
- 21 CFR 211.84(d)(6): Testing and approval or rejection of components, drug product container, and closures
- Sundaram, S, J Eisenhuth, G Howard, and H Brandwein, 1999, Application of Membrane Filtration for Removal of Diminutive Bioburden Organisms in Pharmaceutical Products and Processes, PDA J Pharm Sci Technol, 53(4):186–201
- Kong, F, G James, S Gordon, A Zekynski, and GL Gilbert, 2001, Species-Specific PCR for Identification of Common Contaminant Mollicutes in Cell Culture, Appl Environ Microbiol, 67(7):3195–3200
- Murray, P, E Baron, M Pfaller, F Tenover, and R Yolken, 1995, Manual of Clinical Microbiology, 6th ed., Washington, DC: ASM Press

Date: 5/18/2005

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5. What are the cleaning validation requirements for potent compounds (e.g., compounds that are cytotoxic, mutagenic, or have high pharmacologic activity), and is dedicated equipment required?

Separation or dedication of equipment and facilities for the manufacture of potent compounds is not specifically required by CGMP regulations. However, manufacturers should identify drugs with such risks and define the controls necessary to eliminate risk of product cross-contamination in nondedicated equipment and facilities. Such controls include proper cleaning, cleaning validation, and other contaminant controls. Firms must validate that cleaning procedures are adequate to ensure that cross-contamination does not occur. CGMP regulations establish requirements to guide development and execution of cleaning validation plans.

In designing a facility, firms should carefully evaluate manufacturing processes to determine the best procedural controls and floor plan—optimizing the flow of materials, equipment, and people—to help prevent product contamination.

References:

- 21 CFR 211.42: Design and construction features
- 21 CFR 211.67: Equipment cleaning and maintenance

Date: 6/8/2015

6. How do I perform cleaning validation, including for homeopathic drug products?

21 CFR 211.67(a) requires that any equipment, including dedicated and multipurpose equipment, is "cleaned, maintained, and, as appropriate for the nature of the drug, sanitized and/or sterilized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements." You must therefore ensure that residues (e.g., active ingredients, cleaning agents) are adequately removed from product contact surfaces of all equipment during product changeovers and/or between production campaigns, depending on the types of materials and surfaces in use.

Cleaning procedures should be well-documented and consistent for their intended use. Cleaning validation programs should provide assurance that residues are effectively removed from product contact surfaces, and manufacturers should select test methods that demonstrate their effectiveness. FDA does not provide extensive guidance on conducting cleaning validation but does recommend consulting guidelines published by various trade and professional associations for additional information (e.g., International Society for Pharmaceutical Engineering, Parenteral Drug Association).

Reference:

- 21 CFR 211.67: Equipment cleaning and maintenance

Date: 6/8/2015

7. Does equipment need to be clean enough to meet limits based on the most sensitive possible methods of residue detection or quantification?

No. CGMP regulations require that equipment be cleaned to prevent contamination that "would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements" (see 21 CFR 211.67). The preamble to the CGMP regulations (see 43 FR 45014) indicates that this phrase was added because absolute cleanliness for multiuse equipment is neither valuable nor feasible in many circumstances. The degree of cleanliness needed, therefore, cannot depend on the method of detection because improvements in method sensitivity would necessitate ever-lower limits and ever-increasing wash cycles. Equipment should be as clean as can be reasonably achieved to a residue limit that is documented to be safe, causes no product quality concerns, and leaves no visible residues. Contamination that is reasonably avoidable and removable is never considered acceptable.

References:

- 21 CFR 211.67: Equipment cleaning and maintenance
- Preamble to the Current Good Manufacturing Practice final regulations (43 FR 45014, Sept 29, 1978)External Link Disclaimer

Date: 6/8/2015

8. Do firms need to quantify the total amount of residue remaining on equipment surfaces after manufacturing a product (before cleaning) to support cleaning validation studies?

No. In validating original cleaning procedures, firms need not quantify the level of chemical contamination remaining after manufacturing a product and before cleaning. Firms must, however, ensure that they validate proposed cleaning procedures as for routine use and should not pre-clean or otherwise attempt to make it easier for the procedures being validated to meet their cleaning objectives.

For example, batches significantly smaller than full-scale would not offer sufficient assurance that the cleaning procedure could reliably remove residues to acceptable levels after full-scale production. The material being cleaned should be manufactured at a similar scale and manner as during validation. Also, firms should sample equipment that is stored uncleaned for a longer time than validated to demonstrate that their cleaning procedures are effective.

Once equipment surfaces are cleaned by validated procedures, firms generally are not expected to analytically examine them after each cleaning. (Manual cleaning methods may be an exception to this general rule because of inherent variability in operator compliance and abilities.) However, a residue-monitoring program whose frequency and methods have been determined by risk assessment is recommended.

Reference:

- FDA Guide to Inspections: Validation of Cleaning Processes

Date: 6/8/2015

9. Should laboratory glassware be included in a firm's equipment cleaning validation program?

No. FDA does not expect laboratory glassware to be included in the processing equipment cleaning validation program. Glassware must, of course, be clean, and CGMP regulations consider laboratory equipment to be included within the scope of 21 CFR 211.67. Cleanliness is best assessed by inspecting laboratory procedures for the following:

- Use of nondedicated glassware and other equipment
- Method validation (e.g., ruggedness)
- Absence of extraneous or interfering data in the results of sample analyses

Laboratory cleaning procedures may include repetitive rinses with the solvent used to prepare the analyte, followed by oven drying. The equipment need not be swabbed or otherwise tested to ensure removal of potentially contaminating residues. A firm may elect to sample its glassware for residual contamination to

exclude or explore the possibility of interference in the case of particularly sensitive analyses or difficult-to-clean compounds.

The possibility of carryover contamination affecting a method's performance or integrity of the results is generally considered of low risk to the product and consumers, with the exception of potent compounds. Contaminated laboratory equipment, however, should not be a frequent excuse for rejecting or discarding aberrant results. Glassware that is not properly cleaned can make it difficult to determine if the source of aberrant analytical results is related to the unclean glassware or residues from manufacturing equipment. We expect firms to maintain laboratory equipment in a clean and sanitary manner to provide confidence in the analytical results.

Reference:

- 21 CFR 211.67: Equipment cleaning and maintenance

Date: 6/8/2015

10. What is an acceptable level of detergent residue, and what is the basis for arriving at this level, if any?

It is the firm's responsibility to establish acceptance limits and to be prepared to provide the basis for those limits to FDA. Thus, there is no universal standard for levels of detergent residue. Residues must not exceed their established acceptance limits and must not adversely alter drug product safety, efficacy, quality, or stability (see references below).

References:

- 21 CFR 211.67: Equipment cleaning and maintenance
- FDA Guide to Inspections:Validation of Cleaning Processes

Date: 6/8/2015

11. If a procedure's ability to clean a piece of equipment made of a particular material, such as 316 stainless steel, is acceptable and validated, can that "material-specific" cleaning procedure be applied to other pieces of equipment and compounds without extensive validation?

No. In establishing an effective cleaning procedure for a particular piece of equipment, firms must consider its material of construction/fabrication, exact design, conditions of use, and, in particular, the specific substances that could contaminate the equipment. Therefore, to demonstrate proof of cleaning for a given piece of equipment, firms should have data that relate to all of these factors.

References:

- 21 CFR 211.67: Equipment cleaning and maintenance
- FDA Guide to Inspections:Validation of Cleaning Processes

Date: 6/8/2015

12. Is testing rinse solution enough to support residue determinations for cleaning validation?

No. For cleaning validation, rinse samples alone would not be acceptable; firms should also measure the residue or contaminant on the equipment surface using a direct method (if feasible). One disadvantage of rinse samples is that the rinse solvent may not remove the residue or contaminant. Rinse samples are capable of sampling large surface areas, particularly ones that are difficult to access; therefore, some firms use both swab and rinse samples during the course of their cleaning validation. This is acceptable if the rinse solvent

has been demonstrated to dissolve residues of concern and is otherwise suitable for use on the surfaces to be sampled.

For routine equipment cleaning after validation, a residue-monitoring program whose frequency and methods have been determined by risk assessment is recommended to demonstrate that the validated process continues to consistently clean the equipment.

The purpose of cleaning validation is to demonstrate that a particular cleaning process will consistently clean the equipment to a predetermined standard; the sampling and analytical test methods should be scientifically sound and should provide adequate scientific rationale to support the validation.

References:

- 21 CFR 211.67: Equipment cleaning and maintenance
- FDA Guide to Inspections:Validation of Cleaning Processes

Date: 6/8/2015

13. Does FDA prefer one type of material over another (e.g., polyvinylidene difluoride over stainless steel) for construction of recirculating loops in water for injection (WFI) systems?

No. There is no official agency preference for one material over another. Whatever material a firm selects for its WFI system must be suitable for its intended use. This holds true for virtually all production equipment.

When evaluating the suitability of a WFI system's piping, consider the surface texture or finish of the piping's interior wall (e.g., smoothness, waviness), its ability to resist high temperatures and pressures, and its ability to withstand sterilizing and sanitizing agents and procedures.

Equipment surfaces that are in contact with components, in-process materials, or drug products must not be reactive, additive, or absorptive so as to alter the drug product's safety, identity, strength, quality, or purity beyond its official or established requirements.

References:

- 21 CFR 211.65: Equipment construction
- 21 CFR 211.67: Equipment cleaning and maintenance

Date: 6/8/2015

Control of Components and Drug Product Containers and Closures

1. Do the CGMP regulations permit the destruction of an internal quality assurance audit report once the corrective action has been completed?

The CGMP regulations (21 CFR parts 210 and 211) for finished pharmaceutical manufacturing do not specifically address the requirement to conduct, or to keep records of, internal quality assurance audits. If the report in question was from a routine audit to verify that the firm's quality system is operating as intended, then it would be acceptable if the firm elected to discard the report once all corrections have been verified.

However, any documentation of corrective action as a result of such an audit would have to be retained (see §§ 211.180 and 211.188). For example, if a routine internal audit finds a problem with a mixing step and the outcome is a change in mixing time, all affected procedures, including the master production record, are to reflect the necessary changes, and such records are subject to FDA inspection as usual. Any investigation into

the impact this problem had on related batches is to be retained and also made available for inspection by FDA (see § 211.192).

In addition, any reports of investigations or evaluations prepared in response to, for example, a product complaint (§ 211.198), vendor qualification (§ 211.84), periodic review of records and data (§ 211.180(e)), and a failure investigation (§ 211.192) are not internal audits as discussed above. Such records are subject to FDA inspection and must be retained for at least the time specified in the CGMP regulations (see § 211.180).

References:

- 21 CFR 211.84: Testing and approval/rejection of components, drug product containers, and closures
- 21 CFR 211.180: General requirements
- 21 CFR 211.188: Batch production and control records
- 21 CFR 211.192: Production record review
- 21 CFR 211.198: Complaint files
- Preamble to the Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding regulations (43 FR 45015, paragraph 4, Sept 29, 1978)
- Compliance Policy Guide Sec. 130.300 FDA Access to Results of Quality Assurance Program Audits and Inspections (CPG 7151.02)

2. Can containers, closures, and packaging materials be sampled for receipt examination in the warehouse?

Yes. Generally, we believe that sampling in a typical drug manufacturing facility warehouse would not represent a risk to the container or closure or affect the integrity of the sample results. But whether the act of collecting a sample in the warehouse violates the CGMP requirement that containers "be opened, sampled, and sealed in a manner designed to prevent contamination of their contents..." will depend on the purported quality characteristics of the material under sample and the warehouse environment. For containers or closures purporting to be sterile or depyrogenated, sampling should be under conditions equivalent to the purported quality of the material: a warehouse environment would not suffice (see 21 CFR 211.94 and 211.113(b)). This is to preserve the fitness for use of the remaining containers or closures as well as to ensure sample integrity, if they are to be examined for microbial contamination. At a minimum, any sampling should be performed in a manner to limit exposure to the environment during and after the time samples are removed (i.e., wiping outside surfaces, limiting time that the original package is open, and properly resealing the original package). Well-written and followed procedures are the critical elements.

Note that the CGMP regulations at 21 CFR 211.84 permit a manufacturer to release for use a shipment of containers or closures based on the supplier's certificate of analysis and a visual identification of the containers or closures. Once a supplier's reliability has been established by validation of their test results, a manufacturer could perform the visual examination entirely in the warehouse.

References:

- 21 CFR 211.84: Testing and approval or rejection of components, drug product containers, and closures
- 21 CFR 211.94: Drug product containers and closures
- 21 CFR 211.113(b): Control of microbiological contamination
- 21 CFR 211.122: Materials examination and usage criteria

3. A firm has multiple media fill failures. They conducted their media fills using TSB (tryptic soy broth) prepared by filtration through a 0.2 micron sterilizing filter. Investigation did not show any obvious causes. What could be the source of contamination?

A firm had multiple media fill failures. The media fill runs, simulating the filling process during production, were conducted inside an isolator. The firm used TSB (nonsterile bulk powder) from a commercial source and prepared the sterile solution by filtering through a 0.2 micron sterilizing filter. An investigation was launched to trace the source of contamination. The investigation was not successful in isolating or recovering the contaminating organism using conventional microbiological techniques, including the use of selective (e.g., blood agar) and nonselective (e.g., TSB and tryptic soy agar) media, and examination under a

microscope. The contaminant was eventually identified to be *Acholeplasma laidlawii* by using 16S rRNA gene sequence. The firm subsequently conducted studies to confirm the presence of *Acholeplasma laidlawii* in the lot of TSB used. Therefore, it was not a contaminant from the process, but from the media source.

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Resolution:

For now, this firm has decided to filter prepared TSB, for use in media fills, through a 0.1 micron filter (note: we do not expect or require firms to routinely use 0.1 micron filters for media preparation). In the future, the firm will use sterile, irradiated TSB when it becomes available from a commercial supplier. (Firm's autoclave is too small to permit processing of TSB for media fills, so this was not a viable option.) The firm will continue monitoring for *Mycoplasma* and has revalidated their cleaning procedure to verify its removal. In this case, a thorough investigation by the firm led to a determination of the cause of the failure and an appropriate corrective action.

References:

- 21 CFR 211.113: Control of microbiological contamination
- 21 CFR 211.72: Filters
- 21 CFR 211.84(d)(6): Testing and approval or rejection of components, drug product container, and closures
- Sundaram, S, J Eisenhuth, G Howard, and H Brandwein, 1999, Application of Membrane Filtration for Removal of Diminutive Bioburden Organisms in Pharmaceutical Products and Processes, PDA J Pharm Sci Technol, 53(4):186–201
- Kong, F, G James, S Gordon, A Zekynski, and GL Gilbert, 2001, Species-Specific PCR for Identification of Common Contaminant Mollicutes in Cell Culture, Appl Environ Microbiol, 67(7):3195–3200
- Murray, P, E Baron, M Pfaller, F Tenover, and R Yolken, 1995, Manual of Clinical Microbiology, 6th ed., Washington, DC: ASM Press

Date: 5/18/2005

4. How many containers of each component from each shipment must a firm sample and test to comply with the CGMP regulations for identity testing? Do the CGMP regulations permit the identity test on a pooled, or composite, sample of multiple containers?

The CGMP regulations address component sampling and testing primarily at 21 CFR 211.84. These regulations require representative samples of each shipment of each lot of active and inactive component (or raw materials) to be tested to confirm the identity of the component as labeled prior to release for use in drug product manufacturing. The regulations acknowledge that more than one test may be needed to ascertain a component's identity. For the purpose of this answer, a component's identity is its chemical structure and its physical form (e.g., polymorph, solvate, and appearance) including, if appropriate, its stereochemistry or immunochemistry. (See also ICH guidances for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* and *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*.)

The CGMP regulations do not specify the number of containers to be sampled from each received shipment. However, § 211.84(b) establishes the principles to be followed in designing a sampling program for components. The requirements of this section can be summarized as follows:

- Samples are to be representative of the shipment received.

- The number of containers sampled as well as the amount of material sampled from each container is to be based on statistical criteria for component variability, confidence levels, and the degree of precision required.
- The sample program takes into account the past quality history of the supplier.
- The sample amount is to be sufficient for the necessary analysis and reserve samples.

The first three are most relevant to the question of how many containers to sample for identity testing, i.e., representative sampling, tolerance for variability and confidence required, and past history. (The amount needed for analysis and reserve can be readily met by sampling even one container, so the number of containers is not an important issue once the shipment's identity is verified.)

Unlike most component attributes, a component's identity is generally a discrete variable, i.e., the material in the container either is or is not what the label purports it to be. The component container's content might differ from what the container label states due to mistakes in filling and labeling by the supplier or repacker, or as a result of the substitution of a container's contents during distribution and warehousing before receipt by the drug product manufacturer. Using a wrong component in processing could result in a serious public health hazard. For these reasons, manufacturers need to develop an approach that provides a high degree of confidence that each container in each shipment contains the material purported by the label. (See also 21 CFR 211.160(b), which requires all sampling to be representative and scientifically sound.) The approach must account for the fact that the material's identity must not vary from what is specified. The past quality history of a supplier and the scope of their operations is relevant to the chance for mistakes to occur under a supplier's control, but does not necessarily bear on what happens to a drug once it is outside the supplier's control.

How many containers of each component from each shipment must a firm sample and test to comply with the CGMP requirements for identity testing?

The regulation at § 211.84 requires that representative samples of each shipment of each lot shall be collected for testing. Some manufacturers have interpreted the CGMP regulations to require that each container in a shipment be sampled and tested for the attribute of identity. Testing samples from every container to determine identity may be valuable particularly for components purchased from distributors. (Analytical equipment and methods are readily available that permit rapid, nondestructive identification of material directly in containers in a warehouse area.) The CGMP regulations permit each drug product manufacturer to make its own decision as to the number of containers to sample, as long as the sampling plan is scientifically sound, leads to representative samples, and complies with the principles established at § 211.84(b). An important caveat applies with respect to § 211.84: samples are to be taken by the drug product manufacturer from containers after receipt (i.e., pre-shipment samples or so-called *piggyback* samples are generally not acceptable).

Do the CGMP regulations permit the identity test on a pooled, or composite, sample of multiple containers?

The CGMP regulations address the issue of sample compositing directly but only in the context of individual container sampling. Section 211.84(c)(4) explicitly prohibits compositing samples taken from the top, middle, and bottom of a single container when such stratified sampling is considered necessary (as might be the case when moisture content needs to be controlled, particularly when only a portion of a container may be used in a drug product batch). The preamble for § 211.84(c)(4) explains further that there "is no general prohibition... on compositing samples [from single containers] where such compositing would not mask subdivisions of the sample that do not meet specifications" (see 1978 preambleExternal Link Disclaimer, paragraph 231).

Testing individual samples from multiple containers provides a high level of assurance and is consistent with CGMP. Testing a composite sample for identity could satisfy the CGMP regulations (§§ 211.84 and 211.160) but only if a manufacturer demonstrates either that the detection of a single nonconforming container is not masked by compositing or that an additional test(s) routinely performed on the composite sample ensures that all containers sampled contain the same material. Thus, a purity assay on a composite sample prepared by mixing equal aliquots from each container may be acceptable provided such a test is sufficiently sensitive to reveal the presence of a single nonconforming container.

References:

- Preamble to the Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding regulations (43 FR 45014, Sept 29, 1978)
- 21 CFR 211.82: Receipt and storage of untested components, drug product containers, and closures
- 21 CFR 211.84: Testing and approval or rejection of components, drug product containers, and closures
- 21 CFR 211.160: General requirements (Laboratory Controls)
- FDA Guidance for Industry, 2000, ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances [Text or PDF]
- FDA Guidance for Industry, 1999, ICH Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products [PDF]

5. What methods of analysis are suitable for testing for melamine contamination in pharmaceutical components?

FDA recommends using a method demonstrated to be suitable for detecting melamine adulteration based on the manufacturer's risk assessment and prevention strategy. The manufacturer's selection of a sampling approach and test method sensitivity should address the possibility that (1) melamine might not be uniformly distributed in an at-risk component, or (2) that the source of intentional melamine contamination might be the starting material used to produce the at-risk component. The guidance for industry *Pharmaceutical Components at Risk for Melamine Contamination* provides a link to assay methods capable of detecting melamine at levels as low as 2.5ppm. These methods can detect melamine and cyanuric acid in complex matrices (protein materials) and, therefore, may be useful in developing test methods for other at-risk drug components. FDA also recognizes that a less sensitive method might also be appropriate for screening in certain cases.

References:

- 21 CFR part 211, subpart E: Control of Components and Drug Product Containers and Closures
- FDA Guidance for Industry, 2009, Pharmaceutical Components at Risk for Melamine Contamination

Date: 12/17/2009

6. Does FDA require or recommend any special precautions or controls over the manufacturing of animal-derived drug ingredients to prevent contamination?

Yes, FDA requires that animal-derived ingredients be controlled in a manner to ensure that contamination does not occur, beginning with initial collection and handling of the animal-derived material through its processing and subsequent use in a finished pharmaceutical. See, for example, the Federal Food, Drug, and Cosmetic Act (FD&C Act) sections 501(a)(2)(A) and 501(a)(2)(B).

FDA has special concerns regarding the vulnerability of animal-derived ingredients to contamination by pathogenic agents (i.e., agents that can cause disease or illness in humans or other animals). As background, ingredients are also called *components*, and there are two categories of components used in finished pharmaceutical production: inactive ingredient (often called *excipients*) and active ingredient (often called *active pharmaceutical ingredient (API)*). For the purpose of this guidance, an animal-derived ingredient is a substance of animal origin used to manufacture a drug product. They are primarily derived from byproducts of food production and include extractions from certain animal material and milked animal fluids (e.g., venoms) and may even be human-derived. Products of animal cell cultures, including monoclonal antibodies and therapeutic proteins, are not considered animal-derived APIs for the purpose of this guidance. For additional information concerning biotechnology products, refer to ICH guidance for industry *Q5A Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin*. Ingredient manufacturers are responsible for the quality and safety of the material they produce for use in finished pharmaceuticals. Ingredients are drugs and drugs are required to conform with current good manufacturing practice (FD&C Act, section 501(a)(2)(B)). Finished pharmaceutical manufacturers are also responsible for their selection, qualification, and use of ingredients in finished pharmaceuticals (e.g., the CGMP regulations at 21 CFR part 211, subpart E). Ingredient and finished pharmaceutical manufacturers should fully understand the potential for pathogenic agent contamination beginning with the livestock processing establishment (LPE)

and continuing through subsequent handling and processing, and establish stringent controls to prevent contamination. It is also essential that appropriate tests or examinations are developed and applied to detect contamination as part of any meaningful control program.

References:

- FD&C Act, sections 501(a)(2)(A) and 501(a)(2)(B)
- 21 CFR part 211, subpart E: Control of Components and Drug Product Containers and Closures
- FDA Guidance for Industry, 1998, ICH Q5A Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin

Date: 1/27/2011

7. What are FDA's primary concerns about pathogenic agent contamination of animal-derived drug ingredients?

FDA is concerned about contamination of animal-derived ingredients by pathogenic agents during processing at the LPE, at a subsequent consolidator of animal material or raw material processing plant, or during the manufacturing process to create the final ingredient. One should assume that animal-derived materials will not only harbor but will often support growth of pathogens and accordingly should ensure appropriate control over the handling and processing of these materials. Current good manufacturing practice is to be followed in handling such material to ensure that contamination does not occur that would affect the material's quality and purity, or that would be harmful when the product is administered to patients. Pathogenic agent contamination includes bacteria, molds, viruses, protozoa, parasites, and prions. Pathogenic agents can enter the manufacturing facility within the animal material and contaminate excipients, water, processing equipment, personnel, environment, or packaging. Contaminated drug ingredients present potential health risks that may affect various patient populations, including immune-compromised patients, as well as otherwise healthy people of all ages. An agent may be considered pathogenic if its presence represents a significant risk to patient safety. Factors affecting the pathogenic agent's ability to cause harm include the:

- Nature of the agent (pathogenicity, virulence)
- Amount of the pathogenic agent
- Type of manufacturing process and whether it affects the pathogenic agent's ability to survive
- Ability of the pathogenic agent to grow within the ingredient
- Type of drug product, and its route and length of administration
- Patient population for the drug product (including the most vulnerable patients who may take the drug).

Date: 1/27/2011

8. What manufacturing contamination risks are presented by the different pathogenic agents?

Manufacturing contamination risks presented by the different pathogenic agents can include the following: **Vegetative Bacteria** Vegetative bacteria are actively growing and reproducing bacteria. If there are no steps in the manufacturing process to kill vegetative bacteria, they can proliferate and accumulate during drug ingredient processing. **Toxin-Producing Microorganisms** Several genera and species of microorganisms are capable of producing toxins. Microbial toxins can be divided into two general groups: exotoxins and endotoxins. An exotoxin is a soluble protein excreted by a microorganism, including bacteria, fungi, algae, and protozoa. Exotoxins can include heat-stable toxins that remain active at temperatures as high as 100°C or heat-labile toxins that are readily inactivated by heat treatment. Exotoxins, especially heat-stable exotoxins, can remain in the ingredient throughout the manufacturing process and adversely affect patient health. An endotoxin is a component of the outer membrane of a Gram-negative bacterium. Unlike exotoxins, endotoxins are only released when the organisms are disrupted or destroyed. Endotoxins are heat- and chemical-resistant and, if injected, may induce reactions including febrile effect, hypotension, and shock. **Spore-Forming Bacteria** Spore-forming bacteria can be difficult to eliminate from the manufacturing environment because the spores may be extremely resistant to heat, freezing, extreme pH, desiccation, and chemicals. Spore-forming bacteria can produce exotoxins and can remain dormant without nutrients for extended periods. Spores can be resistant to harsh manufacturing processes that will kill vegetative bacteria. When dormant spores are reintroduced into an acceptable germination environment they

can become active reproductive vegetative cells. Once spores germinate and begin reproducing as vegetative cells, production of exotoxins can occur in a short period of time. **Fungi/Molds** Molds are a subset of fungi that reproduce by releasing spores into the air which, if they land on a moist nutrient source or animal tissue, can germinate. Some species of molds produce toxic byproducts called *mycotoxins*. Mycotoxins can accumulate in animal tissues, rendering the affected organs/tissues unfit for use as a source of starting material for the production of animal-derived drug ingredients. It is important to prevent molds from growing in drug ingredients and when feasible and valuable remove all molds that may contaminate such ingredients. Yeasts, another type of fungi, can also be pathogenic or cause spoilage of an ingredient. **Viruses** Although a virus can only multiply within its host, the inadvertent use of material from virus-infected animals or contact of the drug ingredient with virus-contaminated surfaces can transmit viral particles to patients. Virus survival rates differ based on virus type and variables associated with surface materials that become contaminated. On hard, nonporous surfaces, some virus species can survive and remain transmissible for days or weeks. The probability of an animal virus contaminating an animal-derived ingredient will depend on the viral load of the raw material (e.g., tissue, glands, blood) and the viral clearance capability of the drug ingredient manufacturing process. Both of these factors should be considered when assessing the risk of viral contamination of the ingredient. **Internal Animal Parasites** Transmission of internal parasites occurs from host to host through consumption of contaminated food or water. Parasites live and reproduce within the tissues and organs of infected hosts and are often excreted in feces. Government inspectors are trained to look for internal parasites and prevent unhealthy animals from entering the food supply. Animals deemed fit for food consumption are inspected and certified as healthy. **Prions** Protection from prion contamination includes obtaining bovine meat and meat byproducts from animals not infected with bovine spongiform encephalopathy and protecting against contamination of product with high-risk tissues, especially brain and spinal cord tissue. Drug manufacturers importing bovine material into the United States should be familiar with and adhere to all import eligibility requirements and government regulations pertaining to food and drugs. It is important that farms, slaughterhouses, and renderers observe government regulations prohibiting the use of unhealthy animals in the food supply. Animals deemed fit for food consumption are normally inspected and certified as healthy in many countries.

Date: 1/27/2011

9. What are some ways to minimize pathogenic agent contamination in incoming animal-derived raw material?

The drug component and finished product CGMP guidances and regulations emphasize prevention of problems and avoidance of contamination rather than final testing or examination alone. In other words, control strategies that prevent contamination are central to CGMP, while control strategies based on testing alone do not comply with CGMP regulations. Raw materials from animals can have microbial pathogen health risks based on country of origin, LPE processing, transportation, and manufacturing processing. Under the right circumstances, raw material from animals can provide a suitable (e.g., nutrient-rich) environment for bacteria and mold to proliferate, or for viruses and other pathogenic agents to remain infective. If undetected contaminated raw material enters the manufacturing process, it can remain pathogenic in the product and a hazard to the consumer. The manufacturing conditions used in most ingredient manufacturing processes are often insufficient to eliminate all pathogenic agents from the ingredient. Methods of minimizing contamination of raw material with pathogenic agents may include the following:

- Animal source

  When animal-derived material is used, it is important that it be derived from healthy, disease-free animals. The occurrence of pathogens can vary greatly among different animal species. Ingredient manufacturers should understand the pathogenic risks associated with different animal species and with different organs, glands, or tissues within species. Drug ingredient manufacturers should be aware that even healthy animals can be reservoirs for pathogenic agents and improper handling can spread contamination. If improperly handled, microbial contamination can transfer to uncontaminated tissues and cause contamination.

  Ensuring the health of U.S. livestock is the responsibility of many Federal agencies, most of which are part of the U.S. Department of Agriculture (USDA). Animal-health and food-safety regulations are detailed in titles 9 and 21 of the Code of Federal Regulations. Animal health authorities in each State develop regulations that are consistent with the Federal agencies and are responsible for monitoring and controlling diseases in the State's domestic livestock and poultry. State inspectors ensure

compliance by companies with individual State standards as well as with Federal meat and poultry inspection statutes. States assist in controlling diseases through inspections, testing, vaccinations, treatments, quarantines, and other activities.

Awareness of the conditions of control and monitoring of source animals will aid in determining which animals and animal parts are appropriate for drug product manufacturing.

- LPE

Ingredient manufacturers should consider auditing the LPEs supplying raw materials to them and ensure their compliance with all Federal and State government regulations. It is recommended that manufacturers develop standard operating procedures and define sanitation requirements of raw materials immediately after butchering, including, for example, the following:

  - Chilling requirements, if indicated, including temperature ranges and how soon after butchering chilling should begin
  - Chemical preservation methods, if indicated, including types and concentrations of chemical preservatives used
  - Storage processes, including sanitization of containers and container type/material (e.g., stainless steel vs. food grade plastics)
  - Transportation criteria, including sanitization of containers, if different from storage and temperature ranges

The overall contamination of carcasses with pathogens depends on not only the prevalence and numbers of the pathogens on the hair, skin, and in the intestinal tract of the animal, but is significantly affected by the degree of cross-contamination occurring from these sources during slaughter and processing (see USDA references, below, for additional information). FDA expects that manufacturers will establish appropriate specifications for bioburden in their in-coming raw materials. **References**:

- USDA Animal and Plant Health Inspection Service
- USDA Animal and Plant Health Inspection Service, Import and Export
- USDA Food Safety and Inspection Service, Parasites and Foodborne Illness Fact Sheet

Date: 1/27/2011

10. Are there control measures for minimizing pathogenic agent contamination in animal-derived drug ingredient manufacturing facilities?

Yes, control measures may include the following:

- Process control

Holding and processing times for animal-derived material should be minimized to reduce the likelihood of microbial proliferation. The process qualification studies should include microbial sampling at multiple time points to evaluate the effects of time, temperature, and processing conditions on microbial growth. Routine microbial identification will provide valuable information regarding the types of organisms present in incoming material and throughout the manufacturing process. Processing conditions can then be adjusted to help control the number and types of organisms present during the manufacturing process. Spores and many bacteria can be removed by filtration when filtration or filtration cascade systems are possible. Usually filters with a pore size rating of 0.45 micron or smaller will remove spores and many bacteria from a preparation. Viruses and many toxins are heat labile so a heat treatment should be considered early in process development. Many purification and concentration systems may have antimicrobial effects. The timing and sequence location in the process along with appropriate holding and processing times may serve to optimize the antimicrobial effects of the processes.

Development of process monitoring tests and acceptance criteria should be established during the process development stage.

- Facility and equipment controls

  Facilities can also be reservoirs for pathogenic agents. Maintaining a facility within CGMP should include but not be limited to:

  - Having adequately trained staff
  - Using suitable quality water during manufacturing
  - Having a facility design that minimizes the risk of cross-contamination
  - Providing for proper storage of the ingredient

Cleaning procedures should include cleaning of facilities and equipment that ensures the removal of all raw materials between batches. Designing an effective cleaning program involves setting specific standards, understanding the facility's microbial environmental isolates, and selecting the right disinfecting agents to inactivate isolates that may be in the product or in the environment. Ingredient manufacturers should use sporicidal agents at appropriate intervals in the cleaning schedule to destroy bacterial and fungal spores.

References:

- FDA Guidance for Industry, 2001, ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients
- United States Pharmacopeia (USP) General Information Chapter <1072> Disinfectants and Antiseptics (USP33–NF 28 Reissue, 2010)
- Wiley, JM, L Sherwood, and CJ Woolverton, 2008, Prescott, Harley and Klein's Microbiology, Boston: McGraw-Hill Higher Education.

11. What should drug manufacturers do to prevent formation of glass lamellae (glass fragments) in injectable drugs filled in small-volume glass vials?

Under certain conditions, glass vials can shed thin, flexible fragments called *glass lamellae* (Lachman, Lieberman, et al. 1986; Iacocca, Toltl, et al. 2010). These lamellae are shed from the interior surface of the glass container directly into the drug and are difficult to detect by visual inspection. Several drugs have been recalled due to this problem: epoetin alfa, methotrexate, hyaluronidase recombinant, and fluorouracil (see Enforcement Reports on FDA's Web Site). No adverse events to date have been reported nor can be directly attributed to this phenomenon. However, there is the potential for drugs administered intravenously that contain these fragments to cause embolic, thrombotic, and other vascular events (e.g., phlebitis); and, when administered subcutaneously, to lead to development of foreign body granuloma, local injection site reactions, and increased immunogenicity (Singh, Afonina, et al. 2010). The following conditions have been associated with a higher incidence of the formation of glass lamellae:

- Glass vials manufactured by a tubing process (and thus manufactured under higher heat). These vials are less resistant than molded glass vials and may shed lamellae more easily (Ennis, Pritchard, et al. 2001). The processing conditions used to manufacture glass vials can be designed to mitigate the potential for later delamination.
- Drug solutions formulated at high pH (alkaline) and with certain buffers. Common buffers associated with lamellae formation include citrate and tartrate (Sacha, et al. 2010).
- Length of time the drug product is exposed to the inner surface of the container. The time duration has a direct correlation to the potential for glass lamellae formation to occur during the product shelf life (Lachman, Lieberman, et al. 1986).
- Drug products with room temperature storage requirements. Drugs stored at room temperature have a greater chance of glass lamellae formation than do products stored at colder temperatures (Iacocca and Allgeier 2007).
- Terminal sterilization has a significant effect on glass stability (Iacocca, Toltl, et al. 2010).

The referenced literature, below, includes recommended actions to help prevent the formation of glass lamellae. For example, for products "at risk," the vial surface alkalinity can be minimized by proper selection of glass composition (e.g., highly resistant, nonalkaline earth borosilicate glass), appropriate selection and

qualification of vendors, and proper quality control of the incoming vials. Accordingly, FDA advises drug manufacturers of products to reexamine their supplier quality management program with the glass vial manufacturers to ensure that this phenomenon is not occurring. Further, the Agency reminds finished drug product manufacturers that CGMP regulations require that drug containers not be reactive or additive so as to alter the safety or quality of the drug. See 21 CFR 211.94; Rx-360's Web siteExternal Link Disclaimer, which has commented on the issue of delamination; and deviation reporting regulations for field alert reports (21 CFR 314.81) and biological product deviation reports (21 CFR 600.14). **References**:

- Lachman, L, H Lieberman, and J Kanig, 1986, The Theory and Practice of Industrial Pharmacy, 3rd ed., Philadelphia: Lippincott Williams & Wilkins, 645–649, 796–798
- Iacocca, RG, N Toltl, et al., 2010, Factors Affecting the Chemical Durability of Glass Used in the Pharmaceutical Industry, AAPS Pharm Sci Tech, DOI:10.1208/s12249-010-9506-9
- Singh SK, N Afonina, et al., 2010, An Industry Perspective on the Monitoring of Subvisible Particles as a Quality Attribute for Protein Therapeutics, J Pharm Sci, 99(8):3302–3321
- Ennis RD, R Pritchard, et al., 2001, Glass Vials for Small Volume Parenterals: Influence of Drug and Manufacturing Process on Glass Delamination, Pharm Dev and Tech, 6(3):393–405
- Sacha, G., et al., 2010, Practical Fundamentals of Glass, Rubber, and Plastic Sterile Packaging Systems, Pharm Dev and Tech, 15(1):6–34
- Iacocca, RG, and M Allgeier, 2007, Corrosive Attack of Glass by a Pharmaceutical Compound, J Mater Sci, 42:801–811
- 21 CFR 211.94: Drug product containers and closures
- 21 CFR 314.81: Other postmarketing reports
- 21 CFR 600.14: Reporting of biological product deviations by licensed manufacturers

Date: 3/25/2011

12. Are there any special processing or handling concerns for flexible intravenous (IV) solution bags?

Yes, due to their soft and flexible design, IV solution bags can be easily damaged if not handled properly during processing and labeling. A damaged IV solution bag may not protect the contents from exposure to microbiological contamination as intended. Detection of a damaged IV solution bag by leaks or by examination of the bag may not be possible. In fact, a microscopic defect may not be evident until microbiological contamination becomes visible, which is too late. Prevention of this potentially serious problem is important. FDA is aware of product recalls where IV products in flexible plastic bags were exposed to rough surfaces or sharp objects during labeling, creating microscopic punctures or weakening the bag surfaces. When a compromised IV solution bag is filled with liquid and expands as intended, holes may form at the weak points, leading to a loss of sterility or assurance of sterility.

Manufacturers are reminded that drug product containers and closures must be handled and stored in a manner to prevent contamination (see 21 CFR 211.80(b) and also 211.94).

References:

- 21 CFR 211.80(b): General requirements
- 21 CFR 211.94: Drug product containers and closures

Date: 7/5/2011

13. What can IV drug manufacturers do to help prevent the loss of sterility due to compromised IV solution bag integrity during labeling?

The risk of loss of sterility during labeling can be reduced through the use of nonimpression printing devices for labeling. If a manufacturer uses labeling equipment to apply a label on an IV solution bag and that labeling equipment makes an impression on the IV bag, procedures should be in place to inspect the labeling equipment regularly, particularly after any maintenance is performed. Manufacturing equipment must not have any rough or sharp surfaces that will create punctures or areas of weakness in the IV solution bags. Prevention is important: damaged IV bags may elude detection by standard examinations and tests, including checks for leaks. Manufacturers are reminded that equipment maintenance and cleaning must be

appropriate to prevent malfunctions or contamination that would alter the quality or purity of a drug product (see 21 CFR 211.67).

Additional information: FDA Guidances

- *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*
- *Container Closure Systems for Packaging Human Drugs and Biologics*

References:

- 21 CFR part 211: Current Good Manufacturing Practice for Finished Pharmaceuticals
- 21 CFR 211.22: Responsibilities of quality control unit
- 21 CFR 211.80: General requirements (for the control of components and containers)
- 21 CFR 211.94: Drug product containers and closures
- 21 CFR 211.67: Equipment cleaning and maintenance
- 21 CFR 211.100: Written procedures; deviations

Recall announcementsExternal Link Disclaimer **FDA Warning LettersExternal Link Disclaimer** Date: 7/5/2011

14. Must each batch of a United States Pharmacopeia (USP)-grade API be tested using the analytical procedures specified in the USP monograph?

No; however, in the event of a dispute, the compendial method is considered conclusive (see USP reference, below). Section 201(g) of the FD&C Act includes "articles intended for use as a component" of a finished drug product, including APIs (or drug substances), under its definition of a *drug,* and section 501(b) requires a drug recognized in USP to meet the standards of strength, quality, and purity in the official monograph or to be clearly labeled to designate how it differs from USP standards. Although each batch of a compendial article must conform to the monograph specifications/acceptance criteria, the analytical procedures used to show conformance may differ from official USP methods **if** the alternative methods are fully validated, suitable for use, and give equivalent or better results than the official USP method. All APIs must also be manufactured in compliance with CGMP as stated in section 501(a)(2)(B) of the FD&C Act. **References:**

- FD&C Act Chapter V: Drugs and Devices
- USP 38–National Formulary (NF) 33 (2015) General Notices, Section 6.30

Date: 6/9/2015

15. Who is responsible for analytically testing APIs to ensure they comply with their specifications and with USP requirements, if any? API manufacturers perform analytical testing on APIs to confirm that they meet all applicable specifications established for release. Finished drug product manufacturers ensure that APIs used in their products meet all of their established specifications and—for compendial APIs—meet USP requirements. Additional information is provided below. **API Manufacturer Responsibilities** Section 501(a)(2)(B) of the FD&C Act requires all drugs (including APIs) to be manufactured in compliance with CGMP. FDA therefore expects API manufacturers to follow the recommendations in ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients.* API labeling supplied by the API manufacturer includes a certificate of analysis (COA). Section 11.4 of ICH Q7 recommends that the API manufacturer's COA should include, as applicable, the API's name, grade, batch/lot number, date of release, and a list of "each test performed in accordance with compendial or customer requirements, including the acceptance limits, and the numerical results obtained . . . ." For example, for a compendial-grade API, the COA should identify the compendial tests that were performed (as well as customer-specified tests, if any) and the test results. If a compendial-grade API differs from a USP standard of strength, quality, or purity, that difference should be clearly declared on the label. **Finished Drug Product Manufacturer Responsibilities** In the CGMP regulations for finished pharmaceuticals, 21 CFR 211.80 states that "[T]here shall be written procedures describing in sufficient detail the . . . testing . . . of [finished drug product] components . . . ." Additionally, 21 CFR 211.84(d)(2) states that "[E]ach component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from

the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals." Therefore, if the finished drug product manufacturer accepts the test results from an API supplier's COA rather than performing the tests itself (other than for identity, which the manufacturer is required to perform), the manufacturer must validate the API supplier's reliability. This validation procedure is established by the finished drug product manufacturer and should be consistent with the principles of CGMP and risk management. The finished drug product manufacturer should also ensure that compendial-grade APIs comply with compendial specifications, either by testing the APIs or by validating API suppliers' reliability, as described above. **References:**

- FD&C Act Chapter V: Drugs and Devices
- 21 CFR 211.80: General requirements
- 21 CFR 211.84: Testing and approval or rejection of components, drug product containers and closures
- FDA Guidance for Industry, 2001, ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

Date: 6/9/2015

Production and Process Controls

1. Do the CGMP regulations require a firm to retain the equipment status identification labels with the batch record or other file? Assuming each major piece of equipment has a unique cleaning and use log that is adequately retained, is it acceptable to discard these *quick reference* equipment labels?

The CGMP regulations for finished pharmaceuticals require the retention of cleaning and use logs for non-dedicated equipment, but no similar requirement exists for retaining what are intended to be *quick reference* or temporary status labels. Examples of these kinds of status labels include *mixing lot ###; clean, ready for use as of d/m/y;* and *not clean*. We see no value in the retention of such labels in addition to the required equipment log or batch record documentation. The labels serve a valuable, temporary purpose of positively identifying the current status of equipment and the material under process. Any status label should be correct, legible, readily visible, and associated with the correct piece of equipment. The information on the temporary status label should correspond with the information recorded in the equipment cleaning and use log, or the previous batch record for nondedicated equipment.

Labels are merely one way to display temporary status information about a piece of equipment. It is considered acceptable practice to display temporary equipment status information on dry-erase boards or chalkboards. And it would be appropriate for an FDA investigator to verify that the information on a temporary status label is consistent with the log.

References:

- 21 CFR 211.182: Equipment cleaning and use log
- 21 CFR 211.105: Equipment identification

2. Can containers, closures, and packaging materials be sampled for receipt examination in the warehouse?

Yes. Generally, we believe that sampling in a typical drug manufacturing facility warehouse would not represent a risk to the container or closure or affect the integrity of the sample results. But whether the act of collecting a sample in the warehouse violates the CGMP requirement that containers "be opened, sampled, and sealed in a manner designed to prevent contamination of their contents..." will depend on the purported quality characteristics of the material under sample and the warehouse environment. For containers or closures purporting to be sterile or depyrogenated, sampling should be under conditions equivalent to the purported quality of the material: a warehouse environment would not suffice (see 21 CFR 211.94 and 211.113(b)). This is to preserve the fitness for use of the remaining containers or closures as well as to ensure sample integrity, if they are to be examined for microbial contamination. At a minimum, any sampling

should be performed in a manner to limit exposure to the environment during and after the time samples are removed (i.e., wiping outside surfaces, limiting time that the original package is open, and properly resealing the original package). Well-written and followed procedures are the critical elements.

Note that the CGMP regulations at 21 CFR 211.84 permit a manufacturer to release for use a shipment of containers or closures based on the supplier's certificate of analysis and a visual identification of the containers or closures. Once a supplier's reliability has been established by validation of their test results, a manufacturer could perform the visual examination entirely in the warehouse.

References:

- 21 CFR 211.84: Testing and approval or rejection of components, drug product containers, and closures
- 21 CFR 211.94: Drug product containers and closures
- 21 CFR 211.113(b): Control of microbiological contamination
- 21 CFR 211.122: Materials examination and usage criteria

3. A firm has multiple media fill failures. They conducted their media fills using TSB (tryptic soy broth) prepared by filtration through a 0.2 micron sterilizing filter. Investigation did not show any obvious causes. What could be the source of contamination?

A firm had multiple media fill failures. The media fill runs, simulating the filling process during production, were conducted inside an isolator. The firm used TSB (nonsterile bulk powder) from a commercial source and prepared the sterile solution by filtering through a 0.2 micron sterilizing filter. An investigation was launched to trace the source of contamination. The investigation was not successful in isolating or recovering the contaminating organism using conventional microbiological techniques, including the use of selective (e.g., blood agar) and nonselective (e.g., TSB and tryptic soy agar) media, and examination under a microscope. The contaminant was eventually identified to be *Acholeplasma laidlawii* by using 16S rRNA gene sequence. The firm subsequently conducted studies to confirm the presence of *Acholeplasma laidlawii* in the lot of TSB used. Therefore, it was not a contaminant from the process, but from the media source.

Acholeplasma laidlawii belongs to an order of *Mycoplasma*. *Mycoplasma* contain only a cell membrane and have no cell wall. They are not susceptible to beta-lactams and do not take up Gram stain. Individual organisms are pleomorphic (assume various shapes from cocci to rods to filaments), varying in size from 0.2 to 0.3 microns or smaller. It has been shown that *Acholeplasma laidlawii* is capable of penetrating a 0.2 micron filter, but is retained by a 0.1 micron filter (see Sundaram, Eisenhuth, et al. 1999). *Acholeplasma laidlawii* is known to be associated with animal-derived material, and microbiological media is often from animal sources. Environmental monitoring of *Mycoplasma* requires selective media (PPLO broth or agar).

Resolution:

For now, this firm has decided to filter prepared TSB, for use in media fills, through a 0.1 micron filter (note: we do not expect or require firms to routinely use 0.1 micron filters for media preparation). In the future, the firm will use sterile, irradiated TSB when it becomes available from a commercial supplier. (Firm's autoclave is too small to permit processing of TSB for media fills, so this was not a viable option.) The firm will continue monitoring for *Mycoplasma* and has revalidated their cleaning procedure to verify its removal. In this case, a thorough investigation by the firm led to a determination of the cause of the failure and an appropriate corrective action.

References:

- 21 CFR 211.113: Control of microbiological contamination
- 21 CFR 211.72: Filters
- 21 CFR 211.84(d)(6): Testing and approval or rejection of components, drug product container, and closures
- Sundaram, S, J Eisenhuth, G Howard, and H Brandwein, 1999, Application of Membrane Filtration for Removal of Diminutive Bioburden Organisms in Pharmaceutical Products and Processes, PDA J Pharm Sci Technol, 53(4):186–201

- Kong, F, G James, S Gordon, A Zekynski, and GL Gilbert, 2001, Species-Specific PCR for Identification of Common Contaminant Mollicutes in Cell Culture, Appl Environ Microbiol, 67(7):3195–3200
- Murray, P, E Baron, M Pfaller, F Tenover, and R Yolken, 1995, Manual of Clinical Microbiology, 6th ed., Washington, DC: ASM Press

Date: 5/18/2005

4. Some products, such as transdermal patches, are made using manufacturing processes with higher in-process material reject rates than for other products and processes. Is this okay?

Maybe. It depends on the cause and consistency of the reject rate. Many transdermal patch manufacturing processes produce more waste (i.e., lower yield from theoretical) than other pharmaceutical processes. This should not of itself be a concern. The waste is usually due to the cumulative effect of roll splicing, line start-ups and stoppages, roll-stock changes, and perhaps higher rates of in-process sampling. This is most pronounced for processes involving lamination of rolls of various component layers. Roll-stock defects detected during adhesive coating of the roll, for example, can often only be rejected from the roll after final fabrication/lamination of the entire patch, which contributes to the final process waste stream.

We expect that validated and well-controlled processes will achieve fairly consistent waste amounts batch-to-batch. Waste in excess of the normal operating rates may need (see 21 CFR 21.192) to be evaluated to determine cause (e.g., due to increase in sampling or higher than normal component defects...or both) and the consequences on product quality assessed. We've seen a small number of cases where unusually high intra-batch rejects/losses were due to excessive component quality variability and poorly developed processes.

References:

- 21 CFR 211.100: Written procedures; deviations
- 21 CFR 211.103: Calculation of yield
- 21 CFR 211.110: Sampling and testing of in-process materials and drug products
- 21 CFR 211.192: Production record review

5. Does CGMP regulations require three successful process validation batches before a new active pharmaceutical ingredient (API) or a finished drug product is released for distribution?

No. Neither the CGMP regulations nor FDA policy specifies a minimum number of batches to validate a manufacturing process. The current FDA guidance on APIs (see guidance for industry ICH Q7 for APIs) also does not specify a specific number of batches for process validation.

FDA recognizes that validating a manufacturing process, or a change to a process, cannot be reduced to so simplistic a formula as the completion of three successful full-scale batches. The Agency acknowledges that the idea of three validation batches became prevalent in part because of language used in past Agency guidance. FDA's process validation guidance now recommends a product lifecycle approach. The emphasis for demonstrating validated processes is placed on the manufacturer's process design and development studies in addition to its demonstration of reproducibility at scale, a goal that has always been expected.

However, a minimum number of conformance (a.k.a. validation) batches necessary to validate the manufacturing processes is not specified. The manufacturer is expected to have a sound rationale for its choices in this regard. The Agency encourages the use of science-based approaches to process validation.

In March 2004, FDA revised the Compliance Policy Guide (CPG) Sec. 490.100 on *Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval*. The CPG describes the concept that, after having identified and establishing control of all critical sources of variability, conformance batches are prepared to demonstrate that under normal conditions and operating parameters, the process results in the production of an acceptable product. Successful completion of the initial conformance batches would normally be expected before commercial distribution begins, but some possible exceptions are described in the CPG. For example, although the CPG does not specifically mention concurrent validation for an API in short supply, the Agency would consider the use of concurrent validation when it is necessary to address a true short-supply situation, and if the concurrent validation study conforms to the conditions identified in the CPG (see paragraph 4, a-c).

The conditions outlined in the CPG include expanded testing for each batch intended to address a short-supply situation. Expanded testing conducted according to an established validation protocol could provide added assurance that the batch meets all established and appropriate criteria before the API is used in the finished drug product. Additionally, confidence in the API manufacturing process may be gained by enhanced sampling (larger sample size representative of the batch) and perhaps the testing of additional attributes. Validated analytical methods are needed for testing every batch, including validation batches. The Agency would also expect the manufacturer to use a validation protocol that includes a review and final report after multiple batches are completed, even though the earlier batches may have been distributed or used in the finished drug product.

References:

- 21 CFR 211.100: Written procedures; deviations
- 21 CFR 211.110: Sampling and testing of in-process materials and drug products
- Compliance Policy Guide Sec. 490.100 Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval
- FDA Guidance for Industry, 2001, ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients
- FDA Guidance for Industry, 2011, Process Validation: General Principles and Practices

6. Is it generally acceptable from a CGMP perspective for a manufacturer of sterile drug products produced by aseptic processing to rely solely on ISO 14644-1 and ISO 14644-2 when qualifying its facility?

No. It is generally not acceptable from a CGMP perspective for a manufacturer of sterile drug products produced by aseptic processing to rely solely on ISO [International Organization for Standardization] 14644-1 Part 1: Classification of Air Cleanliness (14644-1) and ISO 14644-2 Part 2: Specifications for Testing and Monitoring to Prove Compliance with ISO 14644-1 (14644-2) when qualifying its facility. Rather, a manufacturer of sterile drug products produced by aseptic processing should use these ISO standards in combination with applicable FDA regulations, guidance, and other relevant references to ensure a pharmaceutical facility is under an appropriate state of control. Consequently, appropriate measures augmenting ISO's recommendations (e.g., with microbiological data) would likely be expected for a firm to meet or exceed CGMP in a pharmaceutical facility.

Please understand that 14644-1 and 14644-2 have superseded Federal Standard 209E, Airborne Particulate Cleanliness Classes in Cleanrooms and Clean Zones (Federal Standard 209E). In November 2001, the U.S. General Services Administration canceled Federal Standard 209E.

Although 14644-1 and 14644-2 are not FDA regulations or FDA guidance, the Agency believes that they are useful in facilitating the international harmonization of industrial air classification for nonviable particle cleanliness in multiple industries (e.g., computer, aerospace, pharmaceutical). As such, FDA adopted these particle cleanliness ratings in the 2004 guidance for industry *Sterile Drug Products Produced by Aseptic Processing–Current Good Manufacturing Practice*. However, due to the unique aspects of producing sterile drug products by aseptic processing (e.g., microbiological issues), an aseptic processing manufacturer should not rely solely on 14644-1 and 14644-2 when qualifying its facility.

References:

- U.S. Food and Drug Administration Web site
- International Organization for Standardization Web siteExternal Link Disclaimer
- ISO 14644-1 Part 1: Classification of Air Cleanliness
- ISO 14644-2 Part 2: Specifications for Testing and Monitoring to Prove Compliance with ISO 14644-1
- FDA Guidance for Industry, 2004, Sterile Drug Products Produced by Aseptic Processing–Current Good Manufacturing Practice
- 21 CFR part 211: Current Good Manufacturing Practice for Finished Pharmaceuticals

7. In 2004, FDA issued a guidance entitled *PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance* that encouraged industry to modernize

manufacturing through enhancements in process control. How can I implement PAT (process analytical technology)?

The objective of FDA's PAT program is to facilitate adoption of PAT. In our 2004 guidance, we discuss FDA's collaborative approach to promote industry uptake of new and beneficial technologies that modernize manufacturing operations and enhance process control. FDA recognizes that firms should be encouraged to promptly implement new systems that improve assurance of quality and process efficiency. Accordingly, our approach to PAT implementation is risk based and includes multiple options:

(1) PAT can be implemented under the facility's own quality system. CGMP inspections by a PAT-certified investigator can precede or follow PAT implementation.

(2) As another quality system implementation option, FDA invites manufacturers to request a preoperational review of their PAT manufacturing facility and process (see ORA Field Management Directive No.135).

(3) A supplement (Changes Being Effected (CBE), CBE-30, or Prior Approval Supplement (PAS)) can be submitted to the Agency prior to implementation, and, if necessary, an inspection can be performed by a PAT-certified investigator before implementation. This option should be used, for example, when an end product testing specification established in the application will be changed.

(4) A comparability protocol can be submitted to the Agency outlining PAT research, validation and implementation strategies, and time lines. Following collaborative review of the general strategy outlined in the comparability protocol, the regulatory pathway can include implementation under the facility's own quality system, a preoperational review, CGMP inspections (either before or after PAT implementation), a combination of these, or another flexible approach.

Manufacturers should evaluate and discuss with the Agency the most appropriate option for PAT implementation (see questions 8 and 9, below).

References:

- FDA Guidance for Industry, 2004, PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance
- ORA Field Management Directive No.135: Pre-operational Reviews of Manufacturing FacilitiesDate Revised: 9/16/2013

8. How do I contact CDER with questions about PAT?

Manufacturers should contact the Office of Pharmaceutical Quality and/or the appropriate review division in CDER to discuss applicability of PAT to CDER-regulated products.

Contact for further information:
CDER Key Officials

Date Revised: 6/18/2015

9. How do I contact CBER with questions about PAT?

Manufacturers should contact the appropriate review division in CBER to discuss applicability of PAT to CBER-regulated products.

Contact for further information:
CBER Key Staff Directory

Date Revised: 9/16/2013

10. What is the acceptable media fill frequency in relation to the number of shifts? Normally, media fills should be repeated twice per shift per line per year. Is the same frequency expected of a process conducted in an isolator?

A firm's justification for the frequency of media fills in relation to shifts should be risk based, depending on the type of operations and the media fill study design. For *closed*, highly automated systems run on multiple shifts, a firm with a rigorous media fill design may be justified to conduct a lower number of total media fill runs. Such a program can be appropriate provided that it still ensures performance of media fills for each aseptic processing line at least semiannually. The 2004 guidance for industry on *Sterile Drug Products Produced by Aseptic Processing* states that "[A]ctivities and interventions representative of each shift, and shift changeover, should be incorporated into the design of the semi-annual qualification program." In addition, the EU Annex 1, *Manufacture of Sterile Medicinal Products,* states that "Normally, process simulation tests should be repeated twice a year per shift and process."

Certain modern manufacturing designs (isolators and *closed vial* filling) afford isolation of the aseptic process from microbiological contamination risks (e.g., operators and surrounding room environment) throughout processing. For such *closed* systems,[1] if the design of the processing equipment is robust and the extent of manual manipulation in the manufacturing process is minimized, a firm can consider this information in determining its media fill validation approach. For example, it is expected that a conventional aseptic processing line that operates on two shifts be evaluated twice per year per shift and culminate in four media fills. However, for aseptic filling conducted in an isolator over two shifts, it may be justified to perform fewer than four media fill runs per year, while still evaluating the line semiannually to ensure a continued state of aseptic process control. This lower total number of media fill runs would be based on sound risk rationale and would be subject to reevaluation if contamination issues (e.g., product nonsterility, media fill failure, any problematic environmental trends) occur.

[l] This does not apply to RABS (restricted access barrier systems).

References:

- 21 CFR 211.63: Equipment design, size, and location
- 21 CFR 211.65: Equipment construction
- 21 CFR 211.67: Equipment cleaning and maintenance
- 21 CFR 211.84(c)(3), which states that "Sterile equipment and aseptic sampling techniques shall be used when necessary."
- 21 CFR 211.113(b), which states that "Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of all aseptic and any sterilization process."
- FDA Guidance for Industry, 2004, Sterile Drug Products Produced by Aseptic Processing
- EU Annex 1, 2003, Manufacture of Sterile Medicinal Products

Date: 12/3/2009

11. Why is FDA concerned about human topical antiseptic drug products?

FDA has identified several incidents of objectionable microbial contamination of topical antiseptic drug products(e.g., alcohol pads or swabs used to prepare the skin prior to an injection) Microbial contamination may be caused by substandard manufacturing practices, and the Agency is concerned about safety risks, such as from infection, associated with this contamination.

Date: 12/21/2011

12. What specific CGMP regulations might be useful to manufacturers of topical antiseptic drug products?

Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act requires all drugs to be manufactured in conformance with CGMP. The CGMP regulations in 21 CFR parts 210 and 211 for finished pharmaceuticals apply equally to over-the-counter (OTC) and prescription (Rx) drug products (see Compliance Policy Guide Sec. 450.100).

The CGMP regulations provide the minimum legal requirements for conducting reliable operations (see 21 CFR part 211). Some relevant CGMP regulations, with a brief description, are given below:

Manufacturing Design and Control: CGMP Requirements and Recommended Guidance for Manufacturers

- **Design manufacturing facilities**(§ 211.42) and processes (see below) to prevent microbial contamination:
  - **For nonsterile drug products**, establish control procedures to monitor output and validate processes to include bioburden testing (§§ 211.110(a)(6)), 211.111) and establish and follow written procedures designed to prevent the introduction of objectionable microorganisms (§ 211.113(a)).
  - **For sterile drug products**, establish and follow written procedures designed to **prevent** microbial contamination (§ 211.113(b)). See the guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*.
- **Conduct process validation studies** to ensure acceptable output (e.g., with topical antiseptics, particularly product microbiological quality) (§ 211.110(a). Implement and validate needed changes when deficient manufacturing steps, equipment, or raw materials may be adversely affecting process control. See the guidance for industry *Process Validation: General Principles and Practices*.
- **Ensure that operating procedures** will consistently produce a quality product (§ 211.100). Review and evaluate any deviations or discrepancies documented during manufacturing and testing to determine if a product lacks assurance of sterility (for sterile antiseptics) or may be contaminated with objectionable microorganisms (for nonsterile antiseptics). Document and implement any corrective actions deriving from the evaluation (§ 211.192).
- **Ensure that all equipment,** including water systems, operates consistently and is clean, sanitary, and suitable for its intended use (§§ 211.63, 211.65, 211.67, and 211.68).
- **Establish and follow in-process bioburden testing** procedures to help monitor in-process control, including understanding the bioburden challenge to a final sterilization process (§ 211.110(a)(6)).

Components, In-Process Materials, Containers or Closures, and Finished Product Testing: CGMP Requirements for Manufacturers

- **Establish appropriate written testing standards/specifications and sampling plans** for components, in-process materials, containers or closures, and finished products (§ 211.160).
- **Establish procedures for testing** and approval or rejection of components, drug product containers, and closures (§ 211.80). Test each lot of a drug product component and container or closure, including those that may be vulnerable to microbiological contamination (§211.84)(d)(4-5), including applicator material (e.g., cotton pads) and water used as an ingredient in the product.
- **Conduct appropriate microbiological tests** before a batch disposition decision is made.Test each batch of a sterile product for sterility (§211.167). Test each batch of a non-sterile product to ensure absence of objectionable microorganisms (§211.165(b)).

Management

The CGMP regulations require that the management of a manufacturing facility maintains a well-functioning quality system, which includes an effective quality unit vested with the responsibilities and authorities required under CGMP (§ 211.22). See ICH guidances for industry *Q9 Quality Risk Management* and *Q10 Pharmaceutical Quality System*.

References:

- Compliance Policy Guide Sec. 450.100 CGMP Enforcement Policy—OTC vs Rx Drugs
- 21 CFR part 211: Current Good Manufacturing Practice for Finished Pharmaceuticals
- FDA Guidance for Industry, 2004, Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice
- FDA Guidance for Industry, 2011, Process Validation: General Principles and Practices
- FDA Guidance for Industry, 2006, ICH Q9 Quality Risk Management
- FDA Guidance for Industry, 2009, ICH Q10 Pharmaceutical Quality System

Date: 12/21/2011

13. How can manufacturers assess and address the risk of microbiological contamination of topical antiseptics?

Because there are potentially many different root causes of product contamination by microorganisms, it is imperative that manufacturers perform a manufacturing risk assessment to understand manufacturing failure modes and implement prevention measures.

In addition, any risk assessment approach should be informed by an understanding of the microbial contamination vulnerabilities of the concerned product.>For example, some product considerations for manufacturers include, but are not limited to:

- Determine the types of microbes that might survive or thrive in your products. Provide additional controls and testing based on the output of the risk assessment to ensure product quality.
- Ensure that your microbial recovery methods are capable of detecting the types of microbes that may affect product quality.
- Evaluate risk of contamination from components, including during component production, storage, or due to the intrinsic risk from source materials. Consider all possible sources of microbial contamination, including the following:
    - Components or products stored in open bins can be at risk for contamination by spore-forming microbes, such as *Bacillus cereus,* as well as by *Serratia* species and other worrisome airborne microbes (see the FDA news release and *Morbidity and Mortality Weekly Report*, referenced below). Manufacturing areas exposed to windy or poor HVAC conditions may increase the potential for this environmental contamination risk.
    - Some materials, especially from natural sources, may have high or objectionable intrinsic bioburden.
    - Water quality can pose a significant risk, as most antiseptics include water as a key ingredient. Contaminated purified water has been the root cause of multiple recalls of antiseptics, including instances of antiseptics contaminated with *Burkholderia* (previously *Pseudomonas*) *cepacia*, an opportunistic pathogen.
    - Unsanitary practices or sources.
    - When manufacturing in areas with high humidity, molds can be of special concern.

References:

- FDA News Release, 2011, FDA Reminds Health Care Professionals About Safe Use of Non-Sterile Alcohol Prep PadsExternal Link Disclaimer
- Centers for Disease Control and Prevention, 2011, Contamination of Alcohol Prep Pads with *Bacillus cereus* Group and *Bacillus* Species, Morbidity and Mortality Weekly Report, 60(11):347

Date: 12/21/2011

14. Can *Leptospira* species penetrate sterilizing-grade filters? If so, what should manufacturers keep in mind in their ongoing lifecycle risk management efforts to ensure microbial control?

FDA is aware of a report of *Leptospira licerasiae* contamination in cell cultures (see Chen, Bergenvin, et al. 2012). There is no indication that this bacterium ultimately contaminated either the finished drug substance or drug product. This bacterium has been found to pass through 0.1 µm pore size rated sterilizing-grade membrane filters. While this specific species was the identified contaminant in this case, other *Leptospira* species also are capable of passing through 0.1 µm pore size rated filters (see Faine 1982). Compendial microbiological test methods typically used in association with upstream biotechnology and pharmaceutical production are not capable of detecting this type of bacteria. Whether this apparently rare contamination risk may be more widespread is unknown, and we are sharing this information so that manufacturers can consider whether this hazard may be relevant to their operations.

Leptospira are Gram-negative aerobic spirochetes that are flexible, highly motile, and spiral-shaped with internal flagella. The bacteria measure 1µm in diameter and 10-20 µm in length. *Leptospira* are obligate aerobes that use oxygen as the electron receptor and long-chain fatty acids as a major source of energy.

While some of the *Leptospira* are harmless fresh-water saprophytes, other species are pathogenic and can cause leptosporosis, a significant disease in humans and animals (Ricaldi, Fouts, et al. 2012; Matthias, Ricaldi, et al. 2008; Bharti, Nally, et al. 2003). Based on current information, *Leptospira* contamination does not appear to occur frequently, and purification steps that follow cell culture in a typical biotechnology operation would be expected to prevent carryover to the finished drug substance.Testing of bulk drug substances produced in the reported cases did not detect the *Leptospira* species, and no evidence of deleterious effects on in-process product were observed in the known case study. However, we are providing this communication to alert manufacturers that these types of bacteria can potentially:

- Penetrate sterilizing-grade membrane filters
- Be present in the manufacturing site environment
- Impact in-process production (e.g., production yields, impurity levels, process performance)
- Go undetected due to the limitations of current compendial bioburden tests in detecting this microbial genus

As a general principle, manufacturers should use sound risk management and be aware of unusual microbiota reported in the literature that may impact their manufacturing processes (e.g., cell culture biotechnology, conventional sterile drug manufacturing). Manufacturers should assess their operations, be aware of potential risks, and apply appropriate risk management based on an understanding of possible or emerging contamination risks (see section 18.3 in ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*). As appropriate, preventive measures should be implemented during the product and process lifecycle. To illustrate, if leptospiral contamination is considered possible, or has occurred, risk mitigation procedures and practices for this microorganism should include at least the following:

1. Review of available published articles from the scientific literature and technical reports by related industry organizations that may provide further understanding on how to mitigate this contamination hazard.
2. Use of molecular or nonconventional microbial monitoring methods at appropriate intervals to detect microbial flora that may exist in processing steps or in the immediate environment, but are not readily detected by current routine methods. Such expanded testing should be used to modify the strategy (e.g., timing, frequency, types of tests) of detection and control in the event of newly identified risk posed by the viable, but not easily cultured, microorganism.

   Examples include:

   a. Use of specialized media such as Ellinghausen McCullough Johnson Harris (EMJH) medium (Ellinghausen and McCullough 1965) or other suitable media (Rule and Alexander 1986). It should be noted that these bacteria typically grow very slowly.
   b. Use of validated polymerase chain reaction (PCR) methods (e.g., as an investigative tool) for rapid screening and detection of spirochete bacteria.
   c. Consideration of special stain techniques or other means to identify the presence of *Leptospira* (Frank and Kohn 1973*)*.
3. Use of conventional approaches. Firms should continue to properly employ basic, standard microbiology laboratory practices to detect contamination. For example, the laboratory should ensure that microscopic examination is part of its routine cell culture process control program, as it provides an important means of detecting microbial contaminants that may not readily grow on conventional media.
4. Implementing such quality risk-management measures into the initial design (i.e., preventive actions) and promptly implementing an appropriate corrective action plan in response to newly identified contamination sources, throughout the life cycle of the product.

References:

- FDA Guidance for Industry, 2001, ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients
- Chen, J, J Bergenvin, R Kiss, G Walker, T Battistoni, P Lufburrow, H Lam, and A Vinther, 2012, Case Study: A Novel Bacterial Contamination in Cell Culture Production—*Leptospira licerasiae*, PDA J Pharm Sci Technol, 66(6):580–591
- Faine, S (ed.), 1982, Guidelines for the Control of Leptospirosis, Geneva: World Health Organization

- Ricaldi, JN, DE Fouts, JD Selengut, DM Harkins, KP Patra, et al., 2012, Whole Genome Analysis of *Leptospira licerasiae* Provides Insight into Leptospiral Evolution and Pathogenicity, PLoS Negl Trop Dis, 6(10):e1853
- Matthias, MA, JN Ricaldi, M Cespedes, MM Diaz, RL Galloway, et al., 2008, Human Leptospirosis Caused by a New Antigenically Unique *Leptopspira* Associated with a *Rattus* Species Reservoir in the Peruvian Amazon, PLoS Negl Trop Dis, 2(4):e213
- Bharti, AR, JE Nally, JN Ricaldi, MA Matthias, MM Diaz, et al., 2003, Leptospirosis: A Zoonotic Disease of Global Importance, Lancet Infect Dis, 3:757–771
- Ellinghausen, HC, and WG McCullough, 1965, Nutrition of *Leptospira pomona* and Growth of 13 Other Serotypes: Fractionation of Oleic Albumin Complex (OAC) and a Medium of Bovine Albumin and Polysorbate 80, Am J Vet, 26:45–51
- Rule Pl, and AD Alexander, 1986, Gellan Gum as a Substitute for Agar in Leptospiral Media, J Clin Microbiol, 23(3):500–504
- Frank S, and J Kohn, 1973, J Amer Med Technology, July–Aug

Date: 12/20/2012

15. FDA withdrew its draft guidance for industry on *Powder Blends and Finished Dosage Units—Stratified In-Process Dosage Unit Sampling and Assessment.* What were the Agency's major concerns with this guidance?

FDA's major concern was that sections V and VII of the withdrawn draft guidance no longer represented the Agency's current thinking, as explained below. Section V (Exhibit/Validation Batch Powder Mix Homogeneity) recommended that at least 3 replicate samples be taken from at least 10 locations in the powder blender, but that only 1 of the 3 replicates be evaluated to assess powder blend uniformity. The Agency currently recommends that *all* replicate samples taken from various locations in the blender be evaluated to perform a statistically valid analysis. This analysis can demonstrate that variability attributable to sample location is not significant and that the powder blend is homogenous. Statistical tools are available to ascertain both the number of replicates and the number of sampling locations across the blender that should be analyzed to conduct a valid analysis. Section VII (Routine Manufacturing Batch Testing Methods) acceptance criteria designated to the Standard Criteria Method and the Marginal Criteria Method were based upon the limits published in the United States Pharmacopeia (USP) General Chapter <905> *Uniformity of Dosage Units*. However, the procedures and acceptance criteria in General Chapter <905> are not a statistical sampling plan and so the results of the procedures should not be extrapolated to larger populations. Therefore, because the procedure and acceptance criteria prescribed in section VII provided only limited statistical assurance that batches of drug products met appropriate specifications and statistical quality control criteria, FDA no longer supports their use for batch release. Currently, there are several standard statistical practices that, if used correctly, can help to ensure compliance with CGMP regulations, including 21 CFR 211.110, 21 CFR 211.160, and 21 CFR 211.165.

References:

- 21 CFR 211.110: Sampling and testing of in-process materials and drug products
- 21 CFR 211.160: General requirements [Laboratory Controls]
- 21 CFR 211.165: Testing and release [of the finished drug product] for distribution

Date: 8/6/2013

16. Why is FDA concerned about proper sampling of powder blends?

The CGMPs require that all sampling plans be scientifically sound and representative of the batch under test (see 21 CFR 211.160(b)). Further, in-process testing of powder blends to demonstrate adequacy of mixing is a CGMP requirement (21 CFR 211.110). Between- and within-location variability in the powder blend is a critical component of finished product quality and therefore should be evaluated. Drug product manufacturers need to use a science- and risk-based sampling approach to ensure (a) adequacy of blend mixing and (b) that sampling of the blend is done at a suitable juncture in the manufacturing process. The sampling and analysis needs to ensure that no differences exist between locations in a blend that could adversely affect finished product quality. Traditional sampling using a powder-thief may have drawbacks and limitations, such as causing disturbance to the powder bed, powder segregation, or other sampling errors. However, powder-thief

sampling remains widely used and provides reliable results in many cases. The Agency encourages firms to adopt more innovative approaches to ensuring adequacy of mixing (see, e.g., the guidance for industry *PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*). If a manufacturer proposes to use a thief sampling method, the reliability of the method should be evaluated as part of analytical methods development.

References:

- FDA Guidance for Industry, 2004, PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

Date: 8/6/2013

17. What are some recommended innovative approaches to ensuring adequacy of mixing of powder blends?

Innovative approaches to consider include, but are not limited to: (a) PAT real-time monitoring and feed-forward controlling of the powder blending process (see the guidance for industry *PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*) and (b) use of statistical process control tools to monitor the powder blending process and to maintain a state of control. When a manufacturer decides to implement PAT or other process-monitoring and control techniques for powder blend homogeneity assessment, its decision should be supported with appropriate data and rationale using a science- and risk-based approach. For example, the effective sample size of powder examined by PAT probes has to be estimated such that the scale of scrutiny of the PAT powder blending monitoring can be justified (Wu, Tawakkul, et al. 2009). The number of PAT probes and their locations also have to be justified. If a scientifically sound PAT monitoring and control strategy is established, it can facilitate the assessment of (a) variability across locations within the powder bed (El-Hagrasy, Morris, et al. 2001), (b) variability over time of one location, and (c) potential correlation between the powder sample and the unit dosage form.

References:

- FDA Guidance for Industry, 2004, PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance
- Wu, H, M Tawakkul, M White, and M Khan, 2009, Quality-by-Design (QbD): An Integrated Multivariate Approach for the Component Quantification in Powder Blends, International Journal of Pharmaceutics, 372(1-2):39–48
- El-Hagrasy, A, H Morris, F D'Amico, et al., 2001, Near-Infrared Spectroscopy and Imaging for the Monitoring of Powder Blend Homogeneity, Journal of Pharmaceutical Sciences, 90(9):1298–1307

Date: 8/6/2013

18. What are the Agency's recommendations regarding in-process stratified sampling of finished dosage units?

Stratified sampling is recommended to be used when the population is known to have several subdivisions (i.e., locations), which may give different results for the quality characteristics measured. The Agency expects that no significant differences should exist between in-process locations that could affect finished product quality. Between- and within-location variability is a critical component of finished product quality and therefore should be evaluated. Please refer to ASTM E2709 and ASTM E2810 for further guidance on establishing acceptance criteria for a stratified sampling plan.

References:

- ASTM Standard E2709, 2014, Standard Practice for Demonstrating Capability to Comply with an Acceptance Procedure, West Conshohocken, PA: ASTM InternationalExternal Link Disclaimer
- ASTM Standard E2810, 2011, Standard Practice for Demonstrating Capability to Comply with the Test for Uniformity of Dosage Units, West Conshohocken, PA: ASTM InternationalExternal Link Disclaimer

Date: 8/6/2013

19. For a nonsterile compendial drug product that includes an antimicrobial preservative in its formulation, may I release and market lots of this drug product with initial out-of-specification total aerobic plate counts if these lots test within specification 2 weeks later?

No. 21 CFR 211.113(a) requires appropriate written procedures to be established and followed during manufacturing to prevent objectionable microorganisms in drug products not required to be sterile. Additionally, the second paragraph of USP General Chapter <51> Antimicrobial Effectiveness Testing reads: Antimicrobial preservatives should not be used as a substitute for good manufacturing practices, solely to reduce the viable microbial population of a nonsterile product, or control the presterilization bioburden of a multidose formulation during manufacturing. Drug manufacturers should not rely on antimicrobial preservatives to reduce initial out-of-specification plate counts to within-specification levels and then market the product. Section 211.165(f) mandates that drug products failing to meet established standards or specifications be rejected. The initial test results exhibiting out-of specification levels of microbes are not disqualified even if subsequent test results are within specifications. In such cases, FDA still expects the manufacturer to reject the drug product based on the initial results. It is also not acceptable for manufacturers to allow an inappropriately long time (e.g., weeks) to pass before testing the product, which might permit the preservative to reduce levels of microbes possibly introduced during manufacture and thus avoid out-of-specification test results. Finally, drug manufacturers should review their manufacturing process to determine procedures or equipment that might introduce contaminating microorganisms into the process or product.

References:

- 21 CFR 211.113: Control of microbiological contamination
- 21 CFR 211.165: Testing and release for distribution
- USP 38–National Formulary (NF) 33 (2015) General Chapter <51> Antimicrobial Effectiveness Testing
- USP 38–NF 33 (2015) General Chapter <61> Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests
- USP 38–NF 33 (2015) General Chapter <62> Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms

Date: 6/11/2015

20. Do pharmaceutical manufacturers need to have written procedures for preventing growth of objectionable microorganisms in drug products not required to be sterile? What does *objectionable* mean anyway?

Yes, CGMP regulations do require these written procedures. 21 CFR 211.113(a) specifies that appropriate written procedures be established and followed to prevent growth of objectionable microorganisms in drug products not required to be sterile. Even though a drug product is not sterile, a firm must follow written procedures that proactively prevent introduction and proliferation of objectionable microorganisms. 21 CFR 211.165(b) states that "[t]here shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms" before it is released for distribution. The meaning of the term *objectionable* needs to be evaluated on a case-by-case basis by each drug manufacturer. The primary meaning relates to microbial contaminants that, based on microbial species, numbers of organisms, dosage form, intended use, patient population, and route of administration, would adversely affect product safety. Microorganisms may be objectionable for several reasons; for example, they:

- Are a known human pathogen
- Adversely affect product stability
- React with, or potentially damage the integrity of, the container closure system (for example, fermentation that creates gaseous pressures sufficient to rupture a product container/closure)
- Interfere with analytical methods or active ingredient bioavailability

Establishing production time limits is an example of a control to prevent growth of objectionable microorganisms. Per 21 CFR 211.111, time limits for the completion of each phase of production, when appropriate, must be established and followed. For example, if a firm finds it necessary to hold a bulk topical or liquid product for several months until it is filled, the firm might establish a holding time limit to help prevent objectionable microbial buildup. Validation and control over microbial content of purified water

systems used in certain topical products are also examples of such procedures (see FDA guidance, referenced below).

References:

- 21 CFR 211.113: Control of microbiological contamination
- 21 CFR 211.165: Testing and release for distribution
- 21 CFR 211.111: Time limitations on production
- FDA Guidance for Industry, 2011, Process Validation: General Principles and Practices

Date: 6/11/2015

21. For drug products formulated with preservatives to inhibit microbial growth, is it necessary to test for preservatives as part of batch release and stability testing?

Yes. Two types of tests are generally used. Initially, firms perform antimicrobial preservative effectiveness testing to determine a minimally effective level of preservative. Once that level has been determined, firms may establish appropriate corresponding analytical test specifications. Firms may then apply the analytical tests for preservative content at batch release and throughout the shelf life of lots on stability.

References:

- 21 CFR 211.165: Testing and release for distribution
- 21 CFR 211.166: Stability testing
- USP 38–NF 33 (2015) General Chapter <51> Antimicrobial Effectiveness Testing

Date: 6/11/2015

22. Is parametric release an appropriate control strategy for sterile drug products that are not terminally sterilized?

No. Parametric release is only appropriate for terminally sterilized drug products. Although both terminally sterilized and aseptically processed drug product batches are required to meet the sterility test requirement (see 21 CFR 211.167(a)) before release to the market, there are inherent differences between the production of sterile drug products using terminal sterilization and aseptic processing.

Products that are terminally sterilized are rendered sterile in their final, sealed units by sterilizers. Discrete physical parameters (e.g., temperature, pressure, and time) are continuously measured and controlled with robust precision and accuracy during processing. Additionally, parametric release incorporates a sterilization load monitor that is integral to satisfying the requirement for a sterility test (see § 211.167(a)) by confirming that the load has been exposed to the prescribed physical conditions. This allows manufacturers to couple adherence to sterilization cycle parameters with a load monitor to determine thermal lethality, thereby directly confirming sterility and substituting for the sterility test.

In contrast, aseptic processes do not subject the final, sealed drug product to a sterilization cycle, and monitoring the sterility hazards to drugs manufactured throughout aseptic manufacturing operations relies on indirect measurements. Sterilization processes (e.g., filtration) for the drug occur before further manipulations that are performed in Class 100 (ISO 5) environments where transient events can present microbial contamination risks during the manufacturing process. Consequently, indirect measurements used in aseptic processing provide limited information to conclude whether a batch is sterile. Even contemporary aseptic operations conducted in closed RABS and isolators can experience sterility and media fill failures, despite the substantial robustness of these technologies over traditional cleanroom and open RABS operations. The sterility test is therefore an essential element to monitor the state of control of an aseptic operation, and it is the last step in a series of fundamental, required controls that collectively contribute to the minimum assurance that a given manufacturing operation produced a drug that meets its sterility claim. The sterility test also protects patients by potentially preventing the distribution of an aseptically processed drug product batch posing serious safety concerns that would not otherwise be readily detected.

All quality control tests, including the sterility test, have limitations. Although the sterility test may not exhaustively assess batch sterility, the sterility test is, nonetheless, a critical component of a comprehensive control strategy that is designed to prevent microbiological contamination of drug products purporting to be sterile (21 CFR 211.113(b)). Innovations in sterility testing (e.g., rapid microbiological methods, genotyping) and the integration of these innovations into manufacturing operations may further improve prompt operational feedback, which can result in significant batch release efficiencies while ensuring equivalent or better ability to detect nonsterility compared with the compendial method. FDA encourages the use of beneficial testing innovations in conjunction with advanced manufacturing technologies (e.g., robotic isolators) to enhance process design and improve both microbial detection and identification.

References:

- 21 CFR 211.167(a): Special testing requirements
- 21 CFR 211.113(b): Control of microbiological contamination
- FDA Guidance for Industry, 2010, Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes
- FDA Guidance for Industry, 2004, Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice
- Compliance Policy Guide (CPG) Sec. 490.200 Parametric Release of Parenteral Drug Products Terminally Sterilized by Moist Heat

Date: 8/11/2023

23. Does FDA consider ophthalmic drug products[1] to be adulterated when they are not manufactured under conditions that ensure sterility throughout their shelf life and, in the case of multidose products, that prevent harmful microbial contamination throughout their in-use period?

Product sterility is a critical quality attribute (CQA) for ophthalmic drug products.[2]Recent cases of microbially contaminated ophthalmic drug products leading to serious injury and death, as well as recent recalls, highlight the importance of product sterility.[3] Manufacturers of drug products, including sterile products offered or intended for ophthalmic use, must comply with CGMP requirements in 21 CFR parts 210 and 211. Failure to comply with these requirements will cause affected products to be deemed adulterated under section 501(a)(2)(B) of the FD&C Act.

Sterile drug products must meet specific CGMP requirements for personnel, buildings and facilities, materials, production and controls, and testing, as appropriate, to ensure product sterility at the time of manufacture and throughout the product's shelf life. FDA has published guidance[4] to provide clarity on how manufacturers can meet CGMP requirements in 21 CFR parts 210 and 211 when manufacturing sterile drug and biological ophthalmic products using aseptic processing. Some of the relevant regulations and guidance applicable to products for ophthalmic use are summarized below.

- Per 21 CFR 211.113(b), there must be appropriate written procedures designed to prevent microbiological contamination that must be established and followed, including the validation of aseptic and sterilization processes.
- Per 21 CFR 211.94(b), drug product container closure systems must provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.
    - As explained in guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*, a container closure system that does not maintain adequate container integrity after it is sealed is unsuitable for sterile products, and safeguards should be implemented to strictly preclude shipment of product that may lack container closure integrity and lead to product nonsterility. Such safeguards could include ensuring suitability and incoming quality of container closure systems, including dose delivery mechanisms, and ensuring that manufacturing equipment for container closure systems is fit for purpose. Validation of container closure system integrity should demonstrate no penetration of microbial contaminants or chemical or physical impurities.[5]
- Per 21 CFR 211.160, 211.165, and 211.166, there must be appropriate testing to demonstrate conformance to product specifications. When preservatives are used to maintain sterility of ophthalmic products in multidose containers,[6] manufacturers should (1) demonstrate that the preservatives have

sufficient bactericidal and fungistatic activity to inhibit growth of microorganisms over the product's shelf life and during use; and (2) test drug products at release and throughout the product's shelf life to confirm they have a sufficient amount of the preservatives to maintain sterility.[7]

- Per 21 CFR 211.167, there are special testing requirements for products purporting to be sterile and/or pyrogen free, specifically use of appropriate laboratory testing to determine conformance to requirements for sterility. This includes testing for microbial contamination and pyrogens or bacterial endotoxins (e.g., release and stability testing of the drug product in the commercially marketed container closure system).

FDA assesses compliance with these and other applicable CGMP requirements through facility inspections under section 704(a)(1) of the FD&C Act, records requests under section 704(a)(4) of the FD&C Act, and other oversight tools. Manufacturers can find additional insight in the guidance for industry *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*, which, although focused on application submission, includes information about the efficacy of sterilization processes.

[1] As defined in guidance for industry *Quality Considerations for Topical Ophthalmic Drug Products* (December 2023).
[2] See 21 CFR 200.50(a)(1).
[3] See FDA's alerts and warnings about eye drops at https://www.fda.gov/drugs/buying-using-medicine-safely/what-you-should-know-about-eye-drops.
[4] See FDA's 2004 guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*.
[5] This is consistent with USP General Chapter <771> *Ophthalmic Products–Quality Tests*.
[6] Liquid ophthalmic products in multidose containers should contain one or more suitable and harmless substances that will inhibit the growth of microorganisms; see 21 CFR 200.50(b). See also USP General Chapter <51> *Antimicrobial Effectiveness Testing*.
[7] USP General Chapter <51> *Antimicrobial Effectiveness Testing*.

References:

- 21 CFR 200.50: Ophthalmic preparations and dispensers
- 21 CFR part 349: Ophthalmic Drug Products for Over-the-Counter Human Use
- 21 CFR part 210: Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General
- 21 CFR part 211: Current Good Manufacturing Practice for Finished Pharmaceuticals
  - 21 CFR 211.94: Drug product containers and closures
  - 21 CFR 211.113: Control of microbiological contamination
  - 21 CFR 211.160: General requirements
  - 21 CFR 211.165: Testing and release for distribution
  - 21 CFR 211.166: Stability testing
  - 21 CFR 211.167: Special testing requirements
- FD&C Act, sections 501 and 704 (21 U.S.C. 351, 374)
- USP General Chapter <51> Antimicrobial Effectiveness Testing
- USP General Chapter <771> Ophthalmic Products–Quality Tests
- USP General Chapter <1211> Sterility Assurance
- FDA Guidance for Industry, 2023, Quality Considerations for Topical Ophthalmic Drug Products
- FDA Guidance for Industry, 2004, Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice
- FDA Guidance for Industry, 1994, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products

Date: 5/22/2024

24. For human cell and gene therapy products, is there a set minimum number of batches that is required for process performance qualification?

No. There is no set minimum number of process performance qualification (PPQ) batches required to support process validation for human cell and gene therapy (CGT) products. While PPQ is a critical step in validating the performance of a commercial manufacturing process, a minimum number of batches is not specified in

biologics licensing requirements (21 CFR 601.20) or CGMP regulations (for example, 21 CFR 211.100 and 21 CFR 211.110).

However, biologics license application (BLA) submissions are expected to include PPQ data, but the amount of PPQ data can be adjusted to circumstances when justified. FDA uses a flexible, science- and risk-based approach to help expedite CGT product development when PPQ production limitations arise.

When PPQ production limitations exist, the number of PPQ batches needed can be determined based on context-specific factors, such as the complexity of the manufacturing process, the levels of control in place, and the manufacturer's overall level of understanding of the product and process. This understanding comes from characterization studies that should be performed during the design of the manufacturing process and the control strategy, and these studies should be documented in the BLA. In addition, manufacturers can document relevant manufacturing experience from other sufficiently similar products and processes.

Investigational new drug (IND) application sponsors who are preparing to validate the manufacturing process of a CGT product are encouraged to contact CBER to discuss their specific circumstances and what flexibilities may apply to validation of their product's manufacturing process.

References:

- 21 CFR 601.20: Biologics licenses; issuance and conditions
- 21 CFR 211.100: Written procedures; deviations
- 21 CFR 211.110: Sampling and testing of in-process materials and drug products
- FDA Guidance for Industry, 2011, Process Validation: General Principles and Practices
- FDA Draft Guidance for Industry, 2024, Frequently Asked Questions - Developing Potential Cellular and Gene Therapy Products

Holding and Distribution

1. What is a recall?

Recalls are actions taken by a firm to remove from the market any product that is in violation of laws administered by FDA. Recalls of a drug may be conducted on a firm's own initiative or by FDA request. A recall is an alternative to an FDA-initiated court action for removing or correcting violative, distributed products (see 21 CFR 7.40(a)). Under FDA's CGMP regulations for finished pharmaceuticals, manufacturers must establish and follow written procedures to facilitate the recall of defective products from the market (see 21 CFR 211.150(b)).

References:

21 CFR 7.40(a): Recall policy
21 CFR 211.150(b): Distribution procedures
Date: 8/9/2010

2. Can FDA mandate a recall of human drugs?

FDA does not have authority to mandate a recall of a human drug, but it can take more authoritative legal actions against manufacturers that persist in marketing a defective product, such as seizure and injunction. A recall is a firm's removal or correction of a marketed product that FDA considers to be in violation of the laws it administers, and against which FDA would otherwise initiate more powerful legal action (see 21 CFR 7.40(c); also see chapter 7 in FDA's Investigations Operations Manual). Thus, manufacturers typically initiate voluntary recalls when a defect is found within a marketed batch to avoid a potentially more significant enforcement action by FDA. References:

21 CFR 7.40(c): Recall policy
FDA, 2014, Chapter 7—Recall Activities, Investigations Operations Manual
Date: 8/9/2010

3. Are over-the-counter (OTC) drugs subject to the same recall provisions as prescription drugs?

Yes, FDA's recall expectations for drugs apply equally to OTC and prescription. The CGMP regulations also apply to all drug products, whether OTC or prescription.

Reference:
Compliance Policy Guide Sec. 450.100 CGMP Enforcement Policy - OTC vs Rx Drugs
Date: 8/9/2010

4. Do manufacturers of OTC products have to report quality defects?

Manufacturers of OTC drugs approved in a new drug application are required to report quality defects (see 21 CFR 314.81). Manufacturers or distributors of OTC monograph drugs (these are drugs that are not approved in a product-specific application) are not required to submit quality defect reports. However, the manufacturer, packer, or distributor whose name appears on the label of an OTC drug without an approved application (i.e., OTC monograph drugs) must submit to FDA any report received of a serious adverse event associated with such drug when used in the United States (see section 760 of the Federal Food, Drug, and Cosmetic Act). Thus, if a serious adverse event is caused by a quality defect, FDA will receive a report about the event (see also the guidance for industry Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed Without an Approved Application.

References:

21 CFR 314.81: Other postmarketing reports
Federal Food, Drug, and Cosmetic Act, section 760
FDA Guidance for Industry, 2009, Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed Without an Approved Application
Date: 8/9/2010

5. Does FDA expect firms to investigate both released and rejected lots for potential recalls?

Yes. Under 21 CFR 211.180(e), manufacturers must establish and follow written procedures for periodically reviewing complaints, recalls, returned or salvaged drug products, and investigations of product discrepancies. Firms must also review an appropriate number of batches, whether approved or rejected, and, where applicable, records associated with the batches, to ensure that all potentially affected product is thoroughly investigated and appropriate follow-up action is taken (21 CFR 211.192).

References:
21 CFR 211.180(e): General requirements
21 CFR 211.192: Production record review
Date: 8/9/2010

6. What happens if a firm does not voluntarily recall a defective product?

FDA expects that a firm will voluntarily recall a drug that is defective or flawed if it could be hazardous to health. Seizure, multiple seizure, or other court action is indicated when a firm refuses to undertake a recall requested by FDA, or where the Agency has reason to believe that a recall would not be effective, determines that a recall is ineffective, or discovers that a violation is continuing (21 CFR 7.40(c)).

References:
21 CFR 7.40(c): Recall policy
Date: 8/9/2010

Laboratory Controls

1. Many leading analytical balance manufacturers provide built-in "auto calibration" features in their balances. Are such auto-calibration procedures acceptable instead of external performance checks? If not, then what should the schedule for calibration be?

The auto-calibration feature of a balance may not be relied upon to the exclusion of an external performance check (21 CFR 211.68). For a scale with a built-in auto-calibrator, we recommend that external performance checks be performed on a periodic basis, but less frequently as compared to a scale without this feature. The

frequency of performance checks depends on the frequency of use of the scale and the criticality and tolerance of the process or analytical step. Note that all batches of a product manufactured between two successive verifications would be affected should the check of the auto-calibrator reveal a problem. Additionally, the calibration of an auto-calibrator should be periodically verified—a common frequency is once a year—using National Institute of Standards and Technology (NIST)-traceable standards or NIST-accredited standards in use in other countries.

References:

- 21 CFR 211.68: Automatic, mechanical, and electronic equipment
- 21 CFR 211.160(b)(4): General requirements (Laboratory Controls)
- United States Pharmacopeia (USP) General Chapter <41> Weights and Balances
- See also ASTM standard E 617, 2013, Standard Specification for Laboratory Weights and Precision Mass Standards, West Conshohocken, PA: ASTM InternationalExternal Link Disclaimer (This standard is incorporated into the USP by reference; other widely recognized standards may be acceptable)

2. Do CGMPs require that forced degradation studies always be conducted of the drug product when determining if a drug product stability test method is stability indicating?

No. Drug product stress testing (forced degradation) may not be necessary when the routes of degradation and the suitability of the analytical procedures can be determined through use of the following:

- Data from stress testing of the drug substance
- Reference materials for process impurities and degradants
- Data from accelerated and long-term studies on the drug substance
- Data from accelerated and long-term studies on the drug product

Additional supportive information on the specificity of the analytical methods and on degradation pathways of the drug substance may be available from literature sources. Section 211.165(e) of the CGMP regulations states that the accuracy, sensitivity, specificity, and reproducibility of test methods shall be established and documented (21 CFR 211.165(e)). Further, 21 CFR 211.166(a)(3) requires that stability test methods be reliable, meaningful, and specific, which means that the content of the active ingredient, degradation products, and other components of interest in a drug product can be accurately measured without interference, often called *stability indicating*. The CGMP regulations do not specify what techniques or tests are to be used to ensure that one's test methods are stability indicating. However, evaluating the specificity of the test methods during forced degradation studies (i.e., exposing the drug to extremes of pH, temperature, oxygen, etc.) of the drug substance and drug product often is necessary to ensure that stability test methods are stability indicating. But in certain circumstances, conducting a forced degradation study of just the drug substance may be sufficient to evaluate the stability-indicating properties of a test method. Generally, in determining whether it is necessary to conduct forced degradation studies of the drug product, the specificity of the test method should be evaluated for its ability to assay drug substance, degradants, and impurities, in the presence of each other, without interference. The evaluation also should provide assurance that there is not a potential for interaction between the drug substance, degradants, impurities, excipients, and container-closure system during the course of the shelf life of the finished drug product. Last, the rationale for any decision made concerning the extent of the forced degradation studies conducted as well as the rationale for concluding that a test method is stability indicating should be fully documented.

References:

- 21 CFR 211.137: Expiration dating
- 21 CFR 211.165(e): Testing and release for distribution
- 21 CFR 211.166(a)(3): Stability testing
- Compliance Policy Guide Sec. 480.100 Requirements for Expiration Dating and Stability Testing (CPG 7132a.04)

3. When performing the USP General Chapter <788> *Particulate Matter in Injections* test for a large volume parenteral (LVP), is it acceptable to take the average among the units tested to determine if the batch meets its specification for this attribute?

No. It is not acceptable to take the average among the LVP units tested in each batch/lot when following this method because the purpose of this method is to measure and limit intra-batch variability.
Particulate matter refers to small, subvisible particles. General Chapter <788> provides two tests for detecting such particulates—light obscuration and microscopic assay. Both are generally accepted for use in testing

LVPs and small volume parenterals (SVP) for the determination of subvisible particulate matter. Normally, samples are first tested by the light obscuration method; if the sample fails the specified limits, the microscopic assay method can then be used. However, the microscopic method can be the sole test if there is a documented technical reason or interference from the product under test that would make the light obscuration method unsuitable or the results invalid.
Confusion about when averaging data is and is not acceptable is probably due to the sample preparation method for the light obscuration test (General Chapter <788>). At least 2, 5-mL aliquots from each sampled unit or the pooled sample (see below) are to be used in the particulate count determination, and the results from these aliquots are to be averaged for comparison with the specification. Note that the average is of the results from examining each aliquot and not between units. (The results of the first aliquot examined by light obscuration are to be discarded, and the subsequent aliquots—2 or more—are retained.) Pooling units prior to analysis is permitted only if the volume in each unit is less than 25 mL, in which case 10 or more units may be pooled. If the volume in the SVP or LVP is 25 mL or more per unit, single units are to be examined by this method (General Chapter <788>).
Results **among** the test units cannot be averaged because particulate matter is assumed to be non-uniformly dispersed throughout the lot. The intent of assessing results from each individual unit is to ensure adequate representation of the lot and to detect potential variation within a lot.
As to the number of individual units to be tested for LVP and SVP units having a volume of 25mL or more, the USP states that the number of units tested depends on "statistically sound sampling plans," and "sampling plans should be based on consideration of product volume, numbers of particles historically found to be present in comparison to limits, particle size distribution of particles present, and variability of particle counts between units." The USP also suggests that the total number of units tested for any given batch may be less than 10 units (for LVP and pooled SVPs) with proper justification. This is consistent with the CGMP requirement for statistical sampling plans (see 21 CFR 211.165).

References:

- 21 CFR 211.160: General requirements (Laboratory Controls)
- 21 CFR 211.165(c)(d): Testing and release for distribution
- USP General Chapter <788> Particulate Matter in Injections
- FDA Guidance for Industry, 2006, Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production

4. Can Total Organic Carbon (TOC) be an acceptable method for detecting residues of contaminants in evaluating cleaning effectiveness?

Yes. Since the publication of the inspection guide on cleaning validation in 1993, a number of studies have been published to demonstrate the adequacy of TOC in measuring contaminant residues.
We think TOC or TC can be an acceptable method for monitoring residues routinely and for cleaning validation. But in order for TOC to be functionally suitable, it should first be established that a substantial amount of the contaminating material(s) is organic and contains carbon that can be oxidized under TOC test conditions. This is not a trivial exercise because we know that some organic compounds cannot be reliably detected using TOC.
TOC use may be justified for direct surface sample testing as well as indirect (rinse water) sample testing. In either case, because TOC does not identify or distinguish among different compounds containing oxidizable carbon, any detected carbon is to be attributed to the target compound(s) for comparing with the established limit. Thus, a firm should limit background carbon (i.e., carbon from sources other than the contaminant being removed) as much as possible. The established limit, or the amount of residue detected for comparison to the specification, should correct for the target material's composition of carbon. As for any cleaning method, recovery studies are necessary (21 CFR 211.160(b)). If TOC samples are being held for long periods of time before analysis, a firm should verify the impact of sample holding time on accuracy and limit of quantitation.

References:

- 21 CFR 211.67: Equipment cleaning and maintenance
- 21 CFR 211.160(b): General requirements (Laboratory Controls)
- USP General Chapter <643> Total Organic Carbon
- FDA Guide to Inspections: Validation of Cleaning Processes

5. Would a paramagnetic or laser oxygen analyzer be able to detect all possible contaminants or impurities in a medical gas?

No. Although paramagnetic and laser oxygen analyzers are very accurate and reliable when calibrated correctly, these types of analyzers can only detect the presence and measure the strength of oxygen. They are unable to detect contaminants or impurities that may be present, such as hydrocarbons or arsenic compounds. The USP monograph test for oxygen does not include an impurity screen, and other analyzers may need to be used. For example, assays for hydrocarbon impurities are routinely conducted during the oxygen manufacturing process even though the USP does not list hydrocarbons as an impurity. Also, alternative methods may be needed to test high-pressure cylinders for cleaning solution residues.

References:

- 21 CFR 211.160: General requirements (Laboratory Controls)
- 21 CFR 211.165: Testing and release for distribution
- USP Monograph: Oxygen
- USP Monograph: Oxygen 93 Percent

6. Can up to 12-month expiration dating be assigned to oral solid and liquid dosage forms repackaged into unit-dose containers based on guidance in the May 2005 draft revision of Compliance Policy Guide Sec. 480.200 *Expiration Dating of Unit Dose Repackaged Drugs* (CPG 7132b.11)?

No. In May 2005, a Notice of Availability of the draft revision of FDA's Compliance Policy Guide Sec. 480.200 *Expiration Dating of Unit-Dose Repackaged Drugs* (CPG 7132b.11) was announced in the *Federal Register*. The draft CPG specifies certain conditions when it may be possible to assign up to 12-month expiration dating to nonsterile solid and liquid oral drug products repackaged into unit-dose containers without conducting new stability studies to support the length of expiration dating on the repackaged products. The draft CPG was prompted by USP standards for assigning up to a 12-month *beyond-use date* to nonsterile solid and liquid oral dosage forms dispensed in unit-dose containers. (*Beyond-use date* is USP's pharmacy dispensing term for specifying a date on a prescription container beyond which a patient should not use the product.) If finalized, FDA's draft CPG would replace the current version of CPG Sec. 480.200. The current version of CPG Sec. 480.200 was finalized in March 1995 and provides conditions under which FDA will not initiate action for assigning up to 6-month expiration dating for drug products repackaged into unit-dose containers without conducting new stability studies.

FDA is conducting a stability study of certain commercially repackaged drugs to determine the suitability of the draft revision of CPG Sec. 480.200. Until the stability study is complete and FDA evaluates all comments submitted to the public docket in response to the May 2005 *Federal Register* Notice of Availability, the Agency does not intend to make a final decision on the draft revision of CPG Sec. 480.200. Consequently, at this time and until FDA announces a final decision on the draft CPG, the current CPG Sec. 480.200, which was finalized in March 1995, is in effect.

References:

- Compliance Policy Guide Sec. 480.200 Expiration Dating of Unit Dose Repackaged Drugs (CPG 7132b.11)
- Draft Guidance on Expiration Dating of Unit-Dose Repackaged Drugs; Availability (70 FR 30953, May 31, 2005)
- 21 CFR 211.137: Expiration dating
- 21 CFR 211.166: Stability testing

7. Is it ever appropriate to use an unvalidated method to test a drug component or product?

The CGMP regulations require the use of validated methods when performing routine testing of raw material, in-process material, and finished products (21 CFR 211.160, 211.165(e), and 211.194) for manufacturing finished drug products. Method validation studies establish proof that a method is suitable for its intended purpose. The purpose is generally to measure a particular material's conformance to an established specification (see the ICH guidance for industry *Q2 (R1) Validation of Analytical Procedures: Text and Methodology).* FDA recognizes, however, that test methods developed based on scientifically sound principles (e.g., sufficient accuracy and precision) but that are not fully validated may be suitable for use in certain instances during an investigation of a potential quality problem or defect. For example, investigation of an atypical impurity or possible contaminant of a drug product or any of its components (e.g., oversulfated

chondroitin sulfate in heparin) may indicate the need for additional methods beyond routine quality control tests. Such testing may be critical to promptly and adequately evaluate the problem and protect public health. Full evaluation of a method's robustness and reproducibility may not initially be feasible or appropriate when conducting tests in certain investigations. When a company, for whatever reason, tests drug components or products using an unvalidated method, it is important to recognize the possibility of greater uncertainty in the test results derived from these unvalidated test methods, as compared to validated test methods. Nevertheless, the resulting data may yield important information indicating the need for prompt corrective action. Accordingly, we expect all such test results on drug components or products to be reviewed to assess the need for follow-up action (21 CFR 211.192 and 211.180(e)).

References:

- 21 CFR part 210: Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General
- 21 CFR part 211: Current Good Manufacturing Practice for Finished Pharmaceuticals
- FDA Guidance for Industry, 2001, ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients
- FDA Guidance for Industry, 1995–1996, ICH Q2 (R1) Validation of Analytical Procedures: Text and Methodology

Date: 1/6/2011

8. Did FDA withdraw the 1987 *Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices*?

Yes, FDA withdrew the 1987 Guideline. The 1987 Guideline is considered obsolete and does not reflect the Agency's current thinking on the topic. Date: 7/12/2011

9. Where can drug manufacturers find information regarding endotoxin testing?

USP publishes endotoxin testing recommendations and acceptance criteria in USP General Chapter <85> *Bacterial Endotoxins Test*. General Chapter <85> provides methods and calculation of limits for drugs. FDA may, as needed, provide additional guidance to clarify the Agency's current thinking on use of Limulus Amebocyte Lysate (LAL), recombinant LAL, and other endotoxin testing methods.

References:

- USP General Chapter <85> Bacterial Endotoxins Test

Date 7/12/2011

10. Is it acceptable to release non-penicillin finished drug products to market if the products may have been exposed to penicillin, as long as the non-penicillin products are tested and no penicillin residue is found?

21 CFR 211.176, Penicillin Contamination, allows marketing of non-penicillin finished drug products if they are tested using the codified method and found not to be contaminated with penicillin. However, it is not acceptable to release the product unless all other applicable CGMP requirements have been met. In some cases, firms inappropriately apply § 211.176 to market products that have not been produced under CGMP. Notably, 21 CFR 211.42(d) requires that manufacturing operations for penicillin drug products be performed in facilities separate from those used for non-penicillin human drug products. Similarly, 21 CFR 211.46(d) requires that air-handling systems for penicillin and non-penicillin drug products be completely separate. For example, if a non-penicillin product is made in a facility that shares equipment or an air-handling system with a penicillin production area (in violation of § 211.46(d)), the non-penicillin product cannot be made CGMP-compliant through testing alone. However, if a door is accidentally left open between a penicillin-dedicated area and other separate production areas, resulting in possible exposure of the other areas to penicillin, testing those other products for penicillin could justify their release for distribution. However, as per 21 CFR 211.165, all sampling plans and acceptance criteria used for testing and release of the non-penicillin product, including any testing for penicillin contamination, must be adequate to ensure the tested product meets all of its specifications.

References:
- 21 CFR 211.176: Penicillin contamination
- 21 CFR 211.42(d): Design and construction features
- 21 CFR 211.46(d): Ventilation, air filtration, air heating and cooling
- 21 CFR 211.165: Testing and release for distribution

Date: 6/17/2015

11. Can a facility that produced penicillin dosage forms be decontaminated and renovated for production of non-penicillin dosage forms, provided there is no further penicillin production in the renovated facility?

Yes; however, decontamination can be extremely difficult. The decontamination process must include scientifically sound studies demonstrating the efficacy of the decontamination agents, extensive and statistically appropriate sampling throughout the areas before and after decontamination to verify cleanliness, and appropriate testing of such samples with a validated analytical method having an appropriate limit of detection. The CGMP regulations in 21 CFR 211.176 require that if a reasonable possibility exists that a non-penicillin drug product has been exposed to cross-contamination with penicillin, the non-penicillin product must be tested for the presence of penicillin and cannot be marketed if detectable levels are found using the codified method. Such a reasonable possibility may be present if decontamination has not been conducted effectively. Although CGMP regulations do not prohibit decontamination and conversion, the difficulty of cleaning up penicillin residues can make the process daunting (see also FDA Guide to Inspections, referenced below).

References:
- 21 CFR 211.176: Penicillin contamination
- FDA Guide to Inspections:Validation of Cleaning Processes

Date: 6/17/2015

12. Is there an acceptable level of penicillin residue in non-penicillin drug products?

No. There is no established safe level of penicillin residue in non-penicillin drug products (see FDA guidance for industry, referenced below). The CGMP regulations in 21 CFR 211.42(d) and 211.46(d) require that penicillin-manufacturing facilities and air-handling systems must be adequately separated from those used to manufacture other drugs. 21 CFR 211.176 states that a non-penicillin drug product must not be marketed if penicillin is found when tested according to the codified procedure. Alternative validated test methods to detect penicillin residues may be used if demonstrated to be equivalent to or better than the referenced method.

References:
- 21 CFR 211.176: Penicillin contamination
- 21 CFR 211.42(d): Design and construction features
- 21 CFR 211.46(d): Ventilation, air filtration, air heating and cooling
- FDA Guidance for Industry, 2013, Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination

Date: 6/17/2015

13. For injectable drugs in multiple-dose containers, is the number of entries to withdraw a dose a factor in determining the expiration date?

Generally, no. Unless the multiple-dose container is labeled to yield a specific number of doses of a stated volume, there is no limit to the number of withdrawals that may be made from a multiple-dose container before the drug is depleted or reaches its expiration date. The primary concern with multiple-dose containers is the potential for contaminating the product during multiple penetrations through the container stopper. Although the expiration date assigned to such products would be based on the stability of the drug product, stability protocols should include requirements for testing and evaluating container-closure integrity. Container-closure integrity testing may include physically testing the closure seal by using a leak test and monitoring the system's ability to prevent microbial contamination. For multiple-dose injection product containers, functionality testing can include a self-sealing capacity test involving multiple penetrations of a hypodermic needle through the container stopper (see USP references below). Furthermore, injectable drug

products in multiple-dose containers are generally formulated with an antimicrobial agent or preservative—or they contain inherently antimicrobial ingredients—and must meet requirements in accordance with the approved application (new drug application/abbreviated new drug application, biologics license application) and/or USP requirements.

References:

- 21 CFR 211.166: Stability testing
- USP 38–NF 33 (2015) General Chapter <1> Injections
- USP 38–NF 33 (2015) General Chapter <381> Elastomeric Closures for Injections
- FDA Guidance for Industry, 1996, ICH Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products
- FDA Guidance for Industry, 2003, ICH Q1A(R2) Stability Testing of New Drug Substances and Products
- FDA Guidance for Industry, 1996, ICH Q1C Stability Testing for New Dosage Forms
- FDA Guidance for Industry, 2013, ANDAs: Stability Testing of Drug Substances and Products
- FDA Guidance for Industry, 2014, ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers
- FDA Guidance for Industry, 2008, Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products

Date: 6/17/2015

14. How long may a firm store in-process/intermediate powder blends and triturations, sustained-release pellets/beads, and tablet cores, absent separate stability studies, before using them in finished drug products?

For in-process/intermediate materials that are chemically and physically stable, a risk- and science-based assessment process can help identify which material attributes and process parameters might affect the critical quality attributes of the finished drug product in which they are to be used. This assessment should be designed to ensure that materials held (under appropriate storage conditions) for a specified period are appropriate for use in manufacturing the finished drug product without having to conduct formal stability studies to verify the holding periods. In some instances, the risk assessment may include sampling and testing the material being held (at the stage determined by the risk assessment) to verify the manufacturing holding period. However, for unstable materials or for materials held longer than the period established in the risk assessment, firms should conduct stability studies according to an approved stability protocol to verify holding periods. The stability studies should include evaluations of the in-process/intermediate materials up to the time of their use in manufacturing a finished drug product and should include long-term monitoring of finished product batches manufactured with the in-process/intermediate materials. In the latter case, until appropriate stability data are generated, firms should calculate the expiration date assigned to finished product batches based on the date of manufacture/release of the in-process/intermediate material rather than on that of the finished product.

References:

- 21 CFR 211.110: Sampling and testing of in-process materials and drug products
- 21 CFR 211.111: Time limitations on production

Date: 6/17/2015

15. What material can be used as instrument calibration standards for chromatographic systems?

For chromatographic systems, instrument calibration standards should be chosen from highly purified materials that are well characterized and can be accurately weighed. Standards can be compendial (from USP) or non-compendial (e.g., from NIST, a chemical supplier, or produced in-house). Substances obtained from a chemical supplier or produced in-house should be purified and characterized using validated purification processes and validated characterization methods. Purification is necessary because impurities can add variation and interfere with analytical methods. Finished dosage forms generally should be avoided as standards because excipients in the finished dosage form may interfere with analysis.

References:

- FDA guidance for industry, 2015, Analytical Procedures and Methods Validation for Drugs and Biologics
- 21 CFR 211.160(b)(4): Instrument calibration
- 21 CFR 211.194(a)(2) and (c): Method validation and reference standards
- USP General Chapter <621> *Chromatography*, section on System Suitability

Date: 8/12/2019

16. What material can be used for system suitability?

FDA expects system suitability to be checked using qualified primary or secondary reference standards and any materials necessary to ensure adequate method performance. A new batch of highly pure reference standard material (e.g., from a chemical supplier or produced in-house) should be qualified against the primary reference standard. Finished dosage forms or APIs that have not been qualified as reference standards should not be used for system suitability testing. Even when API or a finished dosage form has been properly qualified as a reference standard, it should not be used for system suitability testing if it is from the same batch as sample(s) being tested. Written procedures must be established and followed (21 CFR 211.160 and 211.194). All data — including obvious errors and failing, passing, and suspect data — must be in the CGMP records and subject to review and oversight. Records must be complete (e.g., 21 CFR 211.68(b), 211.188, and 211.194) and subjected to adequate review (21 CFR 211.68(b), 211.186(a), 211.192, and 211.194(a)(8)).

References:

- FDA guidance for industry, 2015, Analytical Procedures and Methods Validation for Drugs and Biologics
- FDA guidance for industry, 2018, Data Integrity and Compliance With Drug CGMP: Questions and Answers
- USP General Chapter <621> *Chromatography*, section on System Suitability

Date: 8/12/2019

17. Is it ever appropriate to perform a "trial injection" of samples?

No. FDA has observed at some drug manufacturers the practice of a trial injection where a sample of a lot is injected into the chromatographic system with the intention of obtaining an unofficial result (e.g., passing or failing). This is in contrast to the appropriate practice where an injection of a standard is performed with the sole intention of determining if the chromatographic system is fit for purpose. The injection of trial samples is not acceptable, in part, because all data from analysis of product samples must be retained and reviewed (21 CFR 211.22, 211.165, 211.192, and 211.194). Furthermore, uncertainty about system performance may also suggest a potential insufficiency of the method's design, validation status, analyst training, equipment maintenance, or other fundamental problem(s) in the laboratory that should be promptly corrected.
Column conditioning does not involve injecting a sample from a lot and is not considered a trial injection. When its use is scientifically justified, column conditioning should be fully described in the method validation package as to the conditions needed to make the measurement (i.e., based on data from the method validation) and should be clearly defined in an approved and appropriate procedure. Only validated test methods that demonstrate accuracy, sensitivity, specificity, and reproducibility may be used to test drugs (21 CFR 211.165(e)). Consistent and unambiguous injection nomenclature should be used, and all data from the column conditioning, including audit trail data, should be maintained and subject to review.
Therefore, FDA considers it a violative practice to perform a trial injection (including under the guise of column conditioning). FDA also considers it a violative practice to use an actual sample in *test*, *prep*, or *equilibration* runs as a means of disguising testing into compliance.

References:

- FDA guidance for industry, 2015, Analytical Procedures and Methods Validation for Drugs and Biologics
- 21 CFR 211.194(a)(2): Method validation

Date: 8/12/2019

Records and Reports

1. **Some products, such as transdermal patches, are made using manufacturing processes with higher in-process material reject rates than for other products and processes. Is this okay?**

Maybe. It depends on the cause and consistency of the reject rate. Many transdermal patch manufacturing processes produce more waste (i.e., lower yield from theoretical) than other pharmaceutical processes. This should not of itself be a concern. The waste is usually due to the cumulative effect of roll splicing, line start-ups and stoppages, roll-stock changes, and perhaps higher rates of in-process sampling. This is most pronounced for processes involving lamination of rolls of various component layers. Roll-stock defects detected during adhesive coating of the roll, for example, can often only be rejected from the roll after final fabrication/lamination of the entire patch, which contributes to the final process waste stream.
We expect that validated and well-controlled processes will achieve fairly consistent waste amounts batch-to-batch. Waste in excess of the normal operating rates may need (see 21 CFR 211.192) to be evaluated to determine cause (e.g., due to increase in sampling or higher than normal component defects ... or both) and the consequences on product quality assessed. We've seen a small number of cases where unusually high intra-batch rejects/losses were due to excessive component quality variability and poorly developed processes.

References:

- 21 CFR 211.100: Written procedures; deviations
- 21 CFR 211.103: Calculation of yield
- 21 CFR 211.110: Sampling and testing of in-process materials and drug products
- 21 CFR 211.192: Production record review

2. **Do the CGMP regulations permit the destruction of an internal quality assurance audit report once the corrective action has been completed?**

The CGMP regulations (21 CFR parts 210 and 211) for finished pharmaceutical manufacturing do not specifically address the requirement to conduct, or to keep records of, internal quality assurance audits. If the report in question was from a routine audit to verify that the firm's quality system is operating as intended, then it would be acceptable if the firm elected to discard the report once all corrections have been verified. However, any documentation of corrective action as a result of such an audit would have to be retained (see §§ 211.180 and 211.188). For example, if a routine internal audit finds a problem with a mixing step and the outcome is a change in mixing time, all affected procedures, including the master production record, are to reflect the necessary changes, and such records are subject to FDA inspection as usual. Any investigation into the impact this problem had on related batches is to be retained and also made available for inspection by FDA (see § 211.192).
In addition, any reports of investigations or evaluations prepared in response to, for example, a product complaint (§ 211.198), vendor qualification (§ 211.84), periodic review of records and data (§ 211.180(e)), and a failure investigation (§ 211.192) are not internal audits as discussed above. Such records are subject to FDA inspection and must be retained for at least the time specified in the CGMP regulations (see § 211.180).

References:

- 21 CFR 211.84: Testing and approval/rejection of components, drug product containers, and closures
- 21 CFR 211.180: General requirements
- 21 CFR 211.188: Batch production and control records
- 21 CFR 211.192: Production record review
- 21 CFR 211.198: Complaint files
- Preamble to the Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding regulations (43 FR 45015, paragraph 4, Sept 29, 1978)
- Compliance Policy Guide Sec. 130.300 FDA Access to Results of Quality Assurance Program Audits and Inspections (CPG 7151.02)

3. **Can a firm demonstrate compliance with current good manufacturing practice (CGMP) by relying on records not accessible to FDA?**

No. Records that are needed to demonstrate compliance with current good manufacturing practice (CGMP records) are subject to FDA inspection under section 704(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[1] Consequently, records that are not subject to review and inspection by FDA (which may include

certain records maintained solely outside the quality system[2]) cannot be relied upon to demonstrate compliance with CGMP requirements.

FDA has observed that some firms maintain certain details relating to product quality complaints and investigations (e.g., records related to the details of a discrepancy and its related investigation) only in a record system that they consider largely out of scope of FDA's inspectional authority, such as a human resources (HR) filing system containing personnel data. The HR filing system at a firm may include qualification information for technical and professional personnel performing functions subject to FDA regulation. FDA has the authority to inspect such records to the extent that they relate to adherence to the CGMP requirement for qualified personnel. FDA also has the authority to inspect records related to product quality complaints and investigations. Records related to employee qualifications and product quality complaints and investigations may be included in an HR filing system. However, CGMP records, whether related to training, discrepancies, or related follow-up actions, should not be retained solely in a filing system that a firm considers largely out of scope of FDA's inspectional authority. Records and other information relating to CGMP must be retained (e.g., in an appropriate CGMP records management system) such that records are available for inspection by FDA and subject to FDA's authority to inspect.[3]
A firm may adopt any appropriate filing system that it chooses and may file information FDA has the authority to inspect with records generally excluded from such authority. However, under section 704(a) of the FD&C Act, FDA investigators may ask a firm to provide CGMP records that may be contained in such files. If the firm denies FDA access to such records that the agency has authority to inspect, this may constitute a limitation of inspection under section 501(j) of the FD&C Act. Examples of limiting an inspection include (1) not providing certain requested CGMP records that FDA has authority to inspect on the grounds that such records are inaccessible because they are in an HR or other filing system that a firm considers largely out of scope of FDA's inspectional authority; and (2) not providing certain CGMP records that FDA has authority to inspect because such records were generated by legal counsel and therefore the firm considers they are not obligated to provide such information. Instead, the firm could redact any information that FDA would not have authority to access, review, and copy. See the guidance for industry *Circumstances That Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection*.
11/16/2022

References:

- 21 CFR 211.22: Responsibilities of quality control unit
- 21 CFR 211.84: Testing and approval or rejection of components, drug product containers, and closures
- 21 CFR 211.180: General requirements
- 21 CFR 211.186: Master production and control records
- 21 CFR 211.188: Batch production and control records
- 21 CFR 211.192: Production record review
- 21 CFR 211.194: Laboratory records
- 21 CFR 211.198: Complaint files
- FD&C Act (21 U.S.C. 301), sections 301(e), 501(a) and (j), and 704(a)
- FDA Guidance for Industry, 2014, Circumstances That Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection
- FDA Guidance for Industry, 2006, Quality Systems Approach to Pharmaceutical CGMP Regulations
- FDA Guidance for Industry, 2009, ICH Q10 Pharmaceutical Quality System

[1]It is a prohibited act under section 301(e) of the FD&C Act to refuse to permit access to or to refuse copying of any record as required by section 704(a) of the Act.
[2]See 21 CFR 211.180(c). See also guidance for industry *Quality Systems Approach to Pharmaceutical CGMP Regulations* (September 2006). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[3]See 501(a)(2)(B) and 704(a) of the FD&C Act; see also 21 CFR 211.180 for finished drugs.

4. **How do the part 11 regulations and "predicate rule requirements" (in 21 CFR part 211) apply to the electronic records created by computerized laboratory systems and the associated printed chromatograms that are used in drug manufacturing and testing?**

Some in industry misinterpret the following text from the guidance for industry *Part 11, Electronic Records; Electronic Signatures–Scope and Application* (*Part 11 g*uidance, lines 164-171) to mean that in all cases paper printouts of electronic records satisfy predicate rule requirements in 21 CFR part 211:
Under the narrow interpretation of the scope of part 11, with respect to records required to be maintained under predicate rules or submitted to FDA, when persons choose to use records in electronic format in place of paper format, part 11 would apply. On the other hand, when persons use computers to generate paper printouts of electronic records, and those paper records meet all the requirements of the applicable predicate rules and persons rely on the paper records to perform their regulated activities, FDA would generally not consider persons to be 'using electronic records in lieu of paper records' under §§ 11.2(a) and 11.2(b). In these instances, the use of computer systems in the generation of paper records would not trigger part 11.
The *Part 11* guidance also states (in lines 150-152) that:
Persons must comply with applicable predicate rules, and records that are required to be maintained or submitted must remain secure and reliable in accordance with the predicate rules.
For high performance liquid chromatography (HPLC) and gas chromatography (GC) systems (and other computerized systems involving user inputs, outputs, audit trials, etc.), the predicate rules, such as 21 CFR 211.68 and 211.180(d), require the electronic records themselves to be retained and maintained in accordance with those regulations. Section 211.180(d) requires records to be retained "either as original records or true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records." Section 211.68 further states that: "[H]ard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data are *exact and complete* and that it is secure from alteration, inadvertent erasures, or loss shall be maintained" (emphasis added). The printed paper copy of the chromatogram would not be considered a *true copy* of the entire electronic raw data used to create that chromatogram, as required by § 211.180(d). The printed chromatogram would also not be considered an *exact and complete* copy of the electronic raw data used to create the chromatogram, as required by § 211.68. The chromatogram does not generally include, for example, the injection sequence, instrument method, integration method, or the audit trail, of which all were used to create the chromatogram or are associated with its validity. Therefore, the printed chromatograms used in drug manufacturing and testing do not satisfy the predicate rule requirements in part 211. The electronic records created by the computerized laboratory systems must be maintained under these requirements.
We recognize that there are cases where it could be appropriate for the printed chromatogram to be used within laboratories for the review of test results. Similarly, it also may be acceptable to provide the printed chromatogram during a regulatory inspection or for application review purposes. However, the electronic record must be maintained and readily available for review by, for example, quality control/quality assurance personnel or the FDA investigator.
In summary, decisions on how to maintain records for computerized systems should be based on predicate rule requirements. We recommend that these decisions be supported by a sound risk assessment.

- FDA Guidance for Industry, 2003, Part 11, Electronic Records; Electronic Signatures—Scope and Application
- 21 CFR 211.180(d): General requirements
- 21 CFR 211.68: Automatic, mechanical, and electronic equipment

Date: 8/3/2010

5. **How does FDA interpret the regulations (21 CFR part 211) regarding the establishment of expiry dating for chemicals, reagents, solutions, and solvents?**

Laboratory "reagents, and standard solutions," as referenced in the CGMP regulations at 21 CFR 211.194, includes laboratory chemicals such as solvents (including mobile phases), dry chemicals (salts, primary standards, etc.), and solutions (buffers, acids/bases, quantitative analytical preparations, etc.), whether purchased or prepared in-house. Laboratory reagents and solutions are used in analytical tests of components, in-process materials, and finished products.
If the purchased laboratory reagent or solution includes a manufacturer's suggested use-by or expiry date, that date should be followed. For purchased laboratory reagents and solutions without a "use by" or expiry date, FDA would expect that an assessment be conducted (a literature review may be acceptable) of that specific chemical's or chemical family's stability and that an appropriate use-by or expiry date be determined.
For in-house prepared solutions, such as mobile phases or other nonquantitative solutions, FDA would expect that an assessment be conducted (again, literature review may be acceptable) to determine an appropriate expiry period. However, for in-house prepared solutions used for quantitative analysis, such as sample or standard solutions used in assay or impurity testing or titration solutions, FDA requires that formal stability studies be conducted to determine an appropriate expiry. As mentioned in the ICH guidance for industry *Q2B Validation of Analytical Procedures: Methodology,* the stability of analytical solutions is a typical method

variation that should be evaluated during robustness testing during method validation. Method validation is a CGMP requirement at 21 CFR 211.160(b).
The determined use-by or expiry dates should be documented within a procedure and followed. Procedures for any in-house prepared laboratory solution should include the determined stability timeframe and should instruct that these solutions be labeled with the appropriately determined use-by or expiry date upon preparation and discarded upon expiration.
These principles would also apply to active pharmaceutical ingredient (API) manufacturing and testing sites. The use of "reagents and solutions" and use-by dates are found throughout the ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*.

References:

- CFR 211.160: General requirements
- CFR 211.194: Laboratory records
- FDA Guidance for Industry, 2001, ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, Section 11, Laboratory Controls
- FDA Guidance for Industry, 1996, ICH Q2B Validation of Analytical Procedures: Methodology

Date: 7/19/2011

Returned and Salvaged Drug Products

1. What should a firm do if its drug products or components have been subjected to improper storage conditions such as those caused by a natural disaster?

Drug products that have been subjected to improper storage conditions (including extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation) due, for example, to natural disasters, fires, accidents, or equipment failures shall not be salvaged and returned to the marketplace. Such exposure can pose a serious risk to a drug's identity, strength, quality, purity or safety (see 21 CFR 211.208). This fundamental CGMP principle applies to any component, in-process material, or finished drug product subjected to such conditions. In some cases, there may be substantial and reasonable uncertainty whether a drug was subjected to these conditions. In such a circumstance, it is essential that a firm nonetheless err on the side of caution in its risk assessment to ensure an appropriate lot disposition decision and conduct a rigorous evaluation in accordance with the standards described under § 211.208. When there is reasonable uncertainty whether a drug was subjected to such conditions, salvaging operations may be conducted only if there is evidence from laboratory testing that the drugs meet all applicable standards of identity, strength, quality, and purity, and from inspection that the drugs and their associated packaging were not subject to improper storage conditions as a result of the disaster or accident. When determining whether drugs have been subjected to such improper conditions, a firm's actions should include but not be limited to:

Obtaining supply chain information, including knowing the names and addresses of all suppliers and distributors of a drug (including components and packaging) to determine if there is a reasonable possibility that such materials were stored under improper conditions.
Determining details such as the time frame, duration, nature, scope, and location of exposure as well as identity of all lots potentially subjected to the improper conditions (e.g., ramifications of a natural disaster such as power disruptions should be considered to ensure a complete risk assessment).
Obtaining certification (either on the certificate of analysis or as a separate statement) declaring that drug lots, including components and packaging, were not subjected to improper storage conditions.

References:
21 CFR 211.208: Drug product salvaging

2. What if the improper storage conditions include exposure to toxic fumes or radiation?

Exposure to potentially harmful levels of toxic fumes or radiation is considered to be an improper storage condition (see above). It is essential that firms exercise due diligence to ensure that their drugs were manufactured, processed, packaged, and held under conditions consistent with CGMP. This includes ensuring acceptability of both raw materials and drug products. FDA routinely monitors the quality of marketed drug products, including those imported into the United States. In response to natural disasters, FDA may increase its monitoring and detection capabilities and apply appropriate regulatory action to help ensure the quality and safety of the drug supply.

References:
FDA Public Health Focus, FDA Response to the Fukushima Dai-ichi Nuclear Power Facility Incident
European Commission, 2011, Food Safety: The EU Reinforces Controls on Imports from JapanExternal Link Disclaimer

3. What should be considered in performing an assessment of whether a firm's drug product, or its components or packaging materials, may have been contaminated with radioactive material?

Radioactive materials (radionuclides) release radiation, also called ionizing radiation, as high-energy particles or electromagnetic energy (e.g., gamma rays) as their unstable atoms transition to a more stable state. Low levels of radiation occur naturally in the environment (as background radiation), but elevated levels may occur, for example, during or following a nuclear reactor accident. Radioactive materials released into the environment by such an accident may contaminate drug products, components, or packaging materials. In these circumstances, firms should determine if any of these articles has become contaminated with radionuclides. If a drug product has been subjected to improper storage, including contamination with radioactive material, the product must not be salvaged and returned to the marketplace (21 CFR 211.208). Similarly, contaminated drug components and packaging materials should not be used or salvaged to manufacture drug products. It is important for manufacturers to know the origin and complete supply chain of a drug product, component, or packaging to better enable an assessment for possible contamination arising from, for example, the accidental release of radioactivity.

Some general concerns about radionuclide contamination from nuclear accidents include, but are not limited to, the following:

Drug products and/or components may become contaminated with radionuclides from various sources, including contaminated atmospheric fallout, ground water, soil, or naturally derived raw materials.
A contaminated water supply used in drug manufacture may result in poor-quality products that fail to meet specifications.

Certain dosage forms, such as injectable and inhalable drugs, may present greater risk to patients if contaminated with radionuclides, because these drugs more directly enter into the bloodstream.
Drug products and/or drug components contaminated with radionuclides may result in poor-quality products that fail to meet stability specifications (e.g., reduced efficacy).
Manufacturers of finished drugs must ensure that their products comply with FDA regulations, which includes assurance that the components are of appropriate quality (see, e.g., 21 CFR part 211). In addition, manufacturers of drug components and primary containers must also ensure the quality of their material. FDA expects drug manufacturers and distributors to be extra vigilant and to take enhanced measures to ensure the quality and safety of their drugs that may have been exposed to radioactive contaminants. It may be appropriate for a firm to undertake measures to prevent purchase of at-risk materials as well as to increase testing of incoming components and finished products before final release. See 21 CFR part 211, including:

21 CFR 211.65, Testing and release for distribution
21 CFR 211.84, Testing and approval or rejection of components, drug product containers, and closures
21 CFR 211.94, Drug product containers and closures
21 CFR 211.208, Drug product salvaging

References:

21 CFR part 211: Current Good Manufacturing Practice for Finished Pharmaceuticals
FDA Public Health Focus, FDA Response to the Fukushima Daiichi Nuclear Power Facility Incident

1. Introduction - Scope

#	Date of Approval	Questions	Answers
1.1	**June 2015**	Should GMP according to ICH Q7 be applied for manufacturing Steps before the defined 'API starting material' i.e., Steps not identified in grey in Table 1?	ICH Q7 does not apply to Steps prior to the introduction of the API starting material. However, there is an expectation that an appropriate level of controls suitable for the production of the API starting material should be applied [ICH Q7, Section 1.3]. Normally, the 'API-starting material' is defined in the regulatory filing by the applicant and approved in the regulatory reviewing process. Additional guidance is provided to define and justify 'API starting material' derived from various sources [ICH Q11, Section 5]; for master cell banks, see [ICH Q5B; ICH Q5D].
1.2	**June 2015**	Does ICH Q7 apply to manufacturing Steps for the addition of substance(s) to an API (e.g., to stabilise the API)?	When a mixture is classified in the regulatory filing as an API in a region or country in which it is used in a drug product, ICH Q7 should be applied to the manufacturing of these mixtures [ICH Q7, Section 1.2, 20 – see Glossary for definition of 'API'].

2. Quality Management

#	Date of Approval	Questions	Answers
2.1	**June 2015**	What is meant by 'quality unit(s) independent from production'?	The intent of the term 'independent' is to prevent any conflict of interest and ensure unbiased decision-making regarding quality-related decisions in the organisation structure. The person in the quality unit who is responsible for final decision-making (e.g., batch release decision) should not have responsibilities for production activities [ICH Q7, Section 2.13].
2.2	**June 2015**	Does ICH Q7 expect that the quality unit performs API release testing?	While the quality unit has responsibility for the release of the API, which includes oversight of the testing and results, ICH Q7 does not prescribe specifically who performs testing. 'quality control' in the ICH Q7 Glossary [ICH Q7, Section 20] refers to the activities, not the organisational structure. For examples of quality responsibility related to testing and release, refer to [ICH Q7, Sections 2.13, 2.22, and 11.12]. Appropriate laboratory controls should be followed [ICH Q7, Sections 11.10, 16.10] regardless of who performs the testing.
2.3	**June 2015**	Can other departments outside of the quality unit be held responsible for releasing raw materials and intermediates?	Yes. The quality unit is responsible for establishing a system to release or reject raw materials, intermediates, packaging, and labelling materials. This responsibility cannot be delegated [ICH Q7, Section 2.22(2)]. The system established by the quality unit may allow 'other departments' to release raw materials and intermediates (except intermediates that are for use outside the control of the manufacturer [ICH Q7, Section 2.22(1)] as long as oversight and the overall responsibility of this system remains with the quality unit.

2.4	**June 2015**	Does ICH Q7 expect that sampling be performed by the quality unit?	No. ICH Q7 does not prescribe specifically who should perform the sampling [ICH Q7, Section 2.22]. However, the quality unit has responsibility for reviewing and approving sampling plans [ICH Q7, Section 11.12] and procedures. Sampling should be performed by adequately trained personnel [ICH Q7, Section 3.10] and be appropriately documented as per [ICH Q7, Section 6.52].
2.5	**June 2015**	What should be the frequency of a product quality review?	A product quality review is generally expected annually. Review timeframes can be appropriately adjusted based upon manufacturing and campaign duration with adequate justification. Even if no manufacturing has occurred in the review period, the quality review should be conducted as per section [ICH Q7, Section 2.50] and include stability, returns, complaints, and recalls. For example, a product quality review may encompass more or less than 12 months depending upon product campaign duration [ICH Q7, Section 2.50; ICH Q10, Section 2.6].
2.6	**June 2015**	Should the product quality review of results include trend analysis?	Trend analysis is usually an important element in verifying the consistency of the process as part of the product quality review [ICH Q7, Sections 2.50, 2.51]. Potential tools to use are described in [ICH Q9, Annex I.9].

3. Personnel

#	Date of Approval	Questions	Answers
3.1	**June 2015**	What is the intent of the statement in [ICH Q7, Section 3.12] 'training should be periodically assessed'?	In [ICH Q7, Section 3.12], the statement 'training should be periodically assessed' refers to a system to evaluate if personnel remain proficient and competent in their job tasks and responsibilities, and whether more frequent, additional, or new training is needed and recurring training is up to date.
3.2	**June 2015**	Does ICH Q7 expect the use of a consultant and can a company delegate tasks and/or responsibility to a consultant?	ICH Q7 does not expect the use of a consultant. Consultants may perform delegated tasks and/or provide advice. However, the ultimate responsibility for API quality must not be delegated [ICH Q10, Section 2.7, ICH Q7, Sections 2.2, 3.3].

4.Buildings and Facilities -Containment

#	Date of Approval	Questions	Answers
4.1	**June 2015**	When are dedicated production areas expected?	ICH Q7 expects dedicated production areas for highly sensitising materials such as penicillins and cephalosporins because of the patient risk (e.g., anaphylactic shock to penicillin-allergic patients) from trace amounts of these compounds in other medicines [ICH Q7, Section 4.40]. For materials of an infectious nature or high pharmacological activity or toxicity, a risk-based approach should be used to determine appropriate containment measures, which may include validated inactivation, cleaning and/or dedicated production areas [ICH Q7, Section 4.41].

			While ICH Q7 does not define high pharmacological activity or toxicity, these are generally determined by evaluating relevant animal and human data collected during research and development. Important considerations in this evaluation of pharmacological activity or toxicity may include Occupational Exposure Limit (OEL), Permitted Daily Exposure (PDE), Acceptable Daily Exposure (ADE), Threshold for Toxicological Concerns (TTC), No Observed Adverse Effect Level (NOAEL) [ICH S Guidelines, ICH E2E, Section 2.1.1], and the consequences of cross-contamination [ICH Q9, Section 4.3].
4.2	**June 2015**	To what extent can quality risk management be used in establishing appropriate containment measures to prevent cross-contamination?	The principles of quality risk management [ICH Q9, Annex II.4] should be applied to the design of buildings, facilities and controls for the purpose of containment, taking into consideration the pharmacological/toxicological/chemical/biological properties of the raw material, intermediate and/or API to be handled or manufactured. Appropriate containment measures and controls [ICH Q7, Section 4.42] include but are not limited to the following: • Technical controls (e.g., dedicated production areas, closed/dedicated Heating Ventilation and Air Conditioning (HVAC) system, closed manufacturing systems, use of disposable technologies, design of facility and equipment for containment and ease of cleaning); and • Procedural (organisational) controls (e.g., cleaning, personnel flow, environmental monitoring and training). Monitoring systems are important to check the effectiveness of the containment controls.

5. Process Equipment – Cleaning

#	Date of Approval	Questions	Answers
5.1	**June 2015**	For dedicated equipment, is 'visually clean' acceptable for verification of cleaning effectiveness, (i.e., no expectation for specific analytical determination)?	'Visually clean' may be acceptable for dedicated equipment based on the ability to visually inspect and sufficient supporting data from cleaning studies (e.g., analytical determination to demonstrate cleaning effectiveness) [ICH Q7, Section 12.76]. Equipment should be cleaned at appropriate intervals (e.g., time or number of batches) to prevent build-up and carryover of contaminants (e.g., degradants or objectionable levels of microorganisms) so that they do not adversely alter the quality of the API [ICH Q7, Sections 5.23, 12.7].
5.2	**June 2015**	Should acceptance criteria for residues be defined for dedicated equipment?	Yes. Regardless of whether equipment is dedicated or not, it is expected that acceptance criteria for residues be defined and that the equipment be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants. Intervals can be based on number of batches, product change-over, time, etc. [ICH Q7, Sections 5.22, 5.23, 5.24, 5.25, 8.50]. Cleaning intervals and acceptance criteria should be established based on an understanding of the process/reactions/degradation, taking into account solubility, potency, toxicity, etc. Establishment of acceptance criteria does not necessarily imply sampling and testing after every cleaning. Visual inspection of equipment for cleanliness is an expectation of [ICH Q7, Section 5.21]. Where validation data has confirmed effective cleaning, cleaning

			procedures should be monitored at appropriate intervals [ICH Q7, Section 12.76].
5.3	**June 2015**	Is it expected that equipment cleaning time limits be confirmed in cleaning validation?	Yes. Equipment cleaning is addressed in two sections in ICH Q7. While the cleaning validation [ICH Q7, Section 12.7] does not specifically address time limits for cleaning, [ICH Q7, Section 5.21] indicates that the maximum time between completion of processing and equipment cleaning (dirty hold time) should be established by the company. This maximum established dirty hold time is the time period for which evidence is available to demonstrate that the equipment can still be reliably cleaned. This maximum established dirty hold time is confirmed during the initial cleaning validation and can be extended with appropriate supporting data. While ICH Q7 does not specify the need for time limits between equipment cleaning and use in the next process (clean hold time), [ICH Q7, Section 5.21] does state that written procedures should include instructions for the protection of clean equipment from contamination prior to use and inspection of equipment for cleanliness immediately before use, if practicable.
5.4	**June 2015**	Is it expected that campaign manufacturing be addressed in cleaning validation?	Yes. The cleaning validation section [ICH Q7, Section 12.7] does not specifically address campaign manufacture. However, sections [ICH Q7, Sections 5.23, 8.50] set forth the expectations that equipment be cleaned at appropriate intervals (e.g., time or number of batches) to prevent build-up and carryover of contaminants so that they do not adversely alter the quality of the API. The appropriate interval is confirmed during cleaning validation.

5.5	**June 2015**	At product changeover, are both visual examination and analytical testing necessary to verify that equipment is clean?	Appropriate cleaning validation verifies that the cleaning process is effective. During cleaning validation, both visual examination and analytical testing should be used to verify cleaning effectiveness [ICH Q7, Sections 12.72 to 75]. Once the cleaning process is validated, routine monitoring of cleanliness of equipment at product changeover should include visual inspection [ICH Q7, Section 12.76]. Frequency of analytical testing to verify ongoing effectiveness of the validated cleaning process is determined by the API manufacturer using a risk-based approach. In situations where the cleaning process is not yet validated, both visual examination and analytical testing are expected.

6. Documentation and Records

#	Date of Approval	Questions	Answers
6.1	**June 2015**	What is meant by 'completely distributed' in [ICH Q7, Section 6.13], which states that 'records should be retained for at least 3 years after the batch is completely distributed'?	For APIs with a retest date, [ICH Q7, Section 6.13] states that records related to production, control and distribution should be retained for at least 3 years after the API batch is 'completely distributed', which is understood as the complete distribution of the entire batch of the API by the API manufacturer to the next party in the supply chain. In the case of APIs handled by agents, brokers, traders, distributors, repackers, and relabellers [ICH Q7, Section 17], 'completely distributed' refers to distribution of the received quantity of the batch of API.

			The intent of ICH Q7 is to retain records for the period of time that the API could be on the market in order to investigate any problems and/or product complaints. Based on accepted industry practice at the time ICH Q7 was written, it was not anticipated that a manufacturer would set a retest date longer than 3 years. However, the use of 'at least three years' in this section of ICH Q7 covers longer record retention periods, which is in alignment with the basic GMP principle and/or regional requirements that records be retained for the entire period the material is available on the market. It is good industry practice to consider retaining records for the period of time the drug product(s) in which the API was used may be available on the market.
6.2	**June 2015**	Does a batch numbering system need to be sequential?	No, [ICH Q7, Section 6.51] says only that batch production records should have a unique batch or ID number.
6.3	**June 2015**	Who is responsible for the issuance of batch production records?	[ICH Q7, Section 2.3] does not specify who is responsible for the issuance of batch production records [ICH Q7, Section 6.5] as long as the issuance process is described in writing and approved by the quality unit [ICH Q7, Section 2.21].

7. Materials Management

#	Date of Approval	Questions	Answers
7.1	**June 2015**	Does the phrase 'grouping of containers' have the same meaning in [ICH Q7, Sections 7.20 and 7.24]?	The phrase 'grouping of containers' should be read in the context of each sentence. A grouping of containers refers to multiple containers physically secured by the supplier (e.g., shrink-wrapped pallet, etc.) usually intended for ease of shipment and reconciliation. [ICH Q7, Section 7.20] is referring to incoming visual examination of materials before acceptance into the facility under quarantine. The phrase in [ICH Q7, Section 7.24], 'grouping of containers (batches)' contains an additional word 'batches' because this section is addressing the need to establish batch traceability for the incoming material.
7.2	**June 2015**	What is expected in terms of evaluation of suppliers of materials?	Different phrases are used to describe the expectation for evaluation of suppliers of materials [ICH Q7, Sections 7.11, 7.12, 7.31], including traders, if any. [ICH Q7, Section 7.12] states that all materials are purchased against a specification and from suppliers approved by the quality unit [ICH Q7, Section 7.31]. Prior to approval of any supplier, an evaluation should be conducted using a risk-based approach [ICH Q9, Appendix II.5; ICH Q7, Section 7.31]. More extensive evaluation is needed for suppliers of those materials classified as 'critical' [ICH Q7, Section 7.11].
7.3	**June 2015**	What is meant by 'full analysis' [ICH Q7, Section 7.31] on batches of raw materials to qualify a supplier?	A 'full analysis' should include all tests specified by the user of the raw material in the regulatory filing. In cases where no filing is required, the full analysis should include tests in other formal written specifications issued by the user of the raw material [ICH Q7, 7.31]. A raw material supplier's Certificate of Analysis (CoA) may not necessarily align with the user's specifications.

7.4	**June 2015**	Are on-site audits required in the evaluation of suppliers?	No. An on-site audit is not required; however, an on-site audit could be a useful tool in the evaluation of a supplier. A risk assessment of the material or the service provided can be used to develop an audit strategy and manage the ongoing evaluation of suppliers [ICH Q7, Sections 7.11, 7.31].
7.5	**June 2015**	Which tests are considered to be identity tests?	For incoming production materials, identity tests and related methods should be used as described in the relevant sections of a Pharmacopoeia monograph, in an approved regulatory filing or in an in-house specification (including method/analytical procedure) [ICH Q7, Section 7.30]. When available, a discriminating test should be considered for identification testing. The visual examination of a label or the material is not considered sufficient except in the cases described in [ICH Q7, Section 7.32].
7.6	**June 2015**	Is it possible to extend the expiry date or retest date of a raw material and what is the acceptable practice to determine how long it may be extended for?	Manufacturing and labelling of raw materials for use by API manufacturers is outside the scope of ICH Q7. As such, retest and expiry dates, as defined in ICH Q7, do not strictly apply to raw materials and may be used in a different manner by the raw material supplier. Expiry date, as defined in the glossary of [ICH Q7, Section 20], applies specifically to the API. API manufacturers may re-evaluate [ICH Q7, Section 7.5] and then use a raw material after the 'expiry date' or 'retest date', based on an appropriate scientific and risk-based justification (e.g., understanding of material attributes, testing, and stability). Similar justifications may be used to extend the date by which the material should be re-evaluated. It is the responsibility of the API manufacturer to ensure the raw materials are appropriate for the intended use at the time of use.

8. Production and in-Process Controls

#	Date of Approval	Questions	Answers
8.1	**June 2015**	Can yield ranges defined for the first batch differ from latter batches within a campaign?	Yes. Differing yield ranges [ICH Q7, Section 8.14] may be described and justified in the manufacturing procedure/master batch record explaining the ranges [ICH Q7, Section 6.41]. For example, the first batch in the series of production of batches of the same material (campaign) may leave residual material in the equipment, resulting in a low yield in the first batch and contributing to an increased yield in a subsequent batch of the campaign.
8.2	**June 2015**	What is meant by 'appropriate specifications (of each batch) prior to blending' [ICH Q7, Section 8.41]?	As a principle, no batches with Out of Specification (OOS) results should be blended [ICH Q7, Section 8.41]. Blending is defined in [ICH Q7, Section 8.40]. Individual intermediate and/or API batches should demonstrate conformance with the filed specifications prior to blending. In regions or circumstances where there are intermediates and/or APIs that do not require filing, conformance with the release specification should be demonstrated.

9. Packaging and Identification Labelling of APIs and Intermediates

No Q&A.

10. Storage and Distribution

#	Date of Approval	Questions	Answers
10.1	**June 2015**	What is meant by 'APIs and intermediates can be transferred under quarantine to another unit under the company's control when...' and is this applicable to contract manufacturers?	[ICH Q7, Section 10.20] states 'APIs and intermediates should only be released for distribution to third parties after they have been released by the quality unit(s). APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorised by the quality unit(s) and if appropriate controls and documentation are in place'. The second sentence in [ICH Q7, Section 10.20] describes transport situations that are not considered distribution. It provides for physical movement (transfer but not release) of quarantined material to another unit. This unit can be on the same site, different site (within the same company), or a contract manufacturer (see final paragraph below). The goal of transfer under quarantine is to allow transportation and testing in parallel. Material that is transferred under quarantine is not to be used for further processing until all testing and quality review is complete and the material is released by the quality unit as defined in [ICH Q7, Section 2.22]. This provision for transfer under quarantine is included in ICH Q7 for situations where a company is shipping APIs or intermediates from one unit to another and has both the need to expedite the shipping and the material management system in place to prevent use of the material before full release. Examples of circumstances where transfer under quarantine may be needed include extraordinary supply chain requirement(s) (e.g., short shelf-life), and materials with a lengthy timeframe for required test(s) (e.g., some microbiological tests, etc.). With appropriate oversight as described in [ICH Q10, Section 2.7], including a written agreement as described in [ICH Q7, Section 16.12], and appropriate ongoing controls, a contract manufacturer may be considered a 'unit under the company's control'. There is a joint responsibility by both parties to clearly justify and document the need to transfer the unreleased intermediate or API, and to ensure appropriate control is maintained to prevent use before full release.

11. Laboratory Controls

#	Date of Approval	Questions	Answers
11.1	**June 2015**	What is expected in terms of impurities for APIs extracted from herbal or animal tissue origin [ICH Q7, Section 11.2]?	In cases where the API itself is the extract from an herbal or animal tissue preparation, all constituents of this extract (concomitant constituents) might be considered to be part of the API. Therefore, a production process-related impurity profile (except, for example, solvents used in the process), would generally not be expected. However, for all APIs derived from herbal or animal sources, tests and limits for possible contaminants originating from these sources (e.g., pesticides, mycotoxins, viruses, herbicides, elemental impurities and wrong species) should be established, based on a risk assessment.

			In cases where herbal or animal sources provide material that is further processed to yield a chemically-defined API, all constituents other than the API are considered impurities. In this situation, the API manufacturer would be expected to establish an impurity profile as well as an API release specification that would include impurity limits. In any case, it is the API manufacturer's responsibility to establish batch release specifications for APIs to ensure that they are safe and of high quality, consistent with appropriate regulatory requirements, applicable compendial specifications and regional expectations [ICH Q7, Section 11.21; ICH Q9; ICH Q11].

11.2	**June 2015**	In cases where an API test method is changed, which method should be used for stability studies already in progress?	The company should decide and justify the decision of which method to use. All test methods for stability studies [ICH Q1A] should be validated and demonstrated to be stability indicating prior to use [ICH Q7, Section 11.51]. Any changes to stability test methods should be documented. Applicability of the changes to the existing stability studies should be assessed and may require filing in accordance with regional requirements for post-approval changes [ICH Q7, Section 13.11].
11.3	**June 2015**	When is it acceptable for an API manufacturer to extend an API retest date [ICH Q7, Section 11.6]?	The purpose of a retest date is to ensure that the API is still suitable for use. The API manufacturer can extend the retest date of a specific batch based on good science and long-term stability results for that API and testing of the specific batch that has been stored according to the label conditions. In some regions, regulatory authority approval of the retest date extension for the batch may be required. If an API manufacturer wants to change (i.e., extend) the retest date for future batches of an API, then it should conduct stability testing sufficient to support the change, and include the new retest date and supporting data in a regulatory filing, as determined by regional requirements.
11.4	**June 2015**	What is meant by 'completely distributed' in [ICH Q7, Section 11.71], which indicates reserve/retention samples should be retained for 3 years after the batch is completely distributed by the manufacturer?	'Completely distributed' refers to the distribution of the entire batch of the API by the API manufacturer to the next party in the supply chain. It should be noted that this applies to all parties that physically process or repackage the API [ICH Q7, Section 20 – see Glossary for definition of 'manufacture'). The intent of ICH Q7 is to retain samples for the period of time that the API could be in the market in order to investigate any problems and/or product complaints. Based on accepted industry practice at the time ICH Q7 was written, it was not anticipated that a manufacturer would set a retest date longer than 3 years. It is a basic GMP principle that reserve samples be retained for the entire period the material is available on the market. For example, if a company sets a retest date of 5 years and the API is completely distributed immediately after manufacturing, it was never intended that the reserve sample be destroyed before the 5 year retest date was reached.
11.5	**June 2015**	Why does ICH Q7 permit the use of a packaging system for reserve/retention samples that is 'more protective than the marketed	Unlike stability samples, the purpose of the reserve/retention sample is not to represent the quality of the batch in the market place but to allow future evaluation of the quality of the original API batch (e.g., in evaluation of potential counterfeits, etc.). Therefore, reserve/retention samples may be stored in packaging (and conditions) that better preserve the original state of the API.

		packaging system' [ICH Q7, Section 11.72]?	

12. Validation

#	Date of Approval	Questions	Answers
12.1	**June 2015**	Is the lifecycle approach to process validation acceptable for APIs under ICH Q7?	Yes, ICH Q7 does not preclude the lifecycle approach [ICH Q7, Section 12.10, ICH Q10, ICH Q11].
12.2	**June 2015**	Can the range of a process parameter be expanded based only on a process deviation(s)?	No. However, information from the investigation into a process deviation(s) can be used to support expanding the range of a process parameter. Additional work and studies are normally needed to adequately demonstrate that the expanded range for the process parameter consistently produces API of the necessary quality [ICH Q7, Sections 2.16, 12.11, 13.13].
12.3	**June 2015**	Would additional process validation studies be needed to support a change in the source of an API starting material?	Any change in the API starting material should be assessed for impact on the API manufacturing process and the resulting API quality [ICH Q7, Section 7.14]. Additional validation studies of the API process may be warranted if the change in the API starting material is deemed significant. In most cases, validation would be expected for a different source of the starting material unless otherwise justified [ICH Q7, Sections 12.1, 13.13].
12.4	**June 2015**	Is a retrospective Approach to validation still acceptable?	Prospective validation is normally expected for processes introduced since the publication of ICH Q7. The concept of retrospective validation remains acceptable as an exception for existing, well established products prior to the implementation of ICH Q7 [ICH Q7, Section 12.44]. If regulatory discussions redefine a step as critical, which had previously been considered non-critical, a protocol describing retrospective analysis of data together with the commitment for concurrent or prospective validation may be an option. Regardless of the type of validation, the quality system should confirm the ongoing robustness of the process (e.g., product quality review).

13. Change Control

#	Date of Approval	Questions	Answers
13.1	**June 2015**	Who is responsible for notifying the drug product manufacturer about relevant changes in API manufacturing?	Each party in the supply chain is responsible for transferring information related to quality or regulatory changes to the next customer in the supply chain. The intention is that the information is transferred along the supply chain to the drug product manufacturer in a timely manner [ICH Q7, Sections 13.17, 17.60].

14. Rejection and reuse of materials

#	Date of Approval	Questions	Answers
14.1	**June 2015**	Should rejected materials be stored under physical and secure segregation?	ICH Q7 does not specify a need for physical and secure segregation. Both [ICH Q7, Sections 4.14 and 10.11] include the provision for the use of alternative control systems for storage of rejected material. Whatever control system is used, the purpose should be to prevent the unintentional or unauthorised use of the rejected material [ICH Q7, Sections 7.44, 10.11, 14.1].
14.2	**June 2015**	Does the definition of expiry date in ICH Q7 preclude the rework or reprocess of an expired API?	According to the definition, material should not be used after the expiry date. The original intent of this definition in ICH Q7 was that expired API should not be used in drug product formulation. It may be acceptable to reprocess [ICH Q7, Section 14.2] or rework [ICH Q7, Section 14.3] the expired API where the API manufacturer has all related historical GMP documentation and additional stability data on the reworked or reprocessed API. There may be registration/filing considerations that are beyond the scope of ICH Q7 in addition to the GMP considerations.
14.3	**June 2015**	Is validation expected for the recovery of material from mother liquor?	It depends. Recovery of material(s) from mother liquor is a process and the need for validation should be assessed as for any other process step [ICH Q7, Section 14.40]. Recovery of material from mother liquor in any process step that must be controlled within predetermined criteria to ensure the API meets its specification is, by definition, a critical process step and should be validated. For example, recovery of API from mother liquor would be considered a critical process step and should be validated [ICH Q7, Sections 12.11, 12.12, 14.41, 14.43, 20 – see Glossary for definitions of 'critical', 'materials', 'mother liquor', and 'validation'].

15. Complaints and Recalls

#	Date of Approval	Questions	Answers
15.1	**June 2015**	Can quality defects of released APIs that are identified by another entity belonging to the same company be handled outside of the API manufacturer's complaint procedure?	Yes. After the release of an API for further use, any identified quality defect should be investigated and addressed according to the API manufacturer's complaint system or equivalent (i.e., non-conformance, deviations, etc.) [ICH Q7, Sections 15.10 to 15.12]. Where equivalent systems are used, such defects should be categorised in a manner that provides clear visibility that the defect was discovered after being released by the API site.
15.2	**June 2015**	Must a quality related return, at the request of the API manufacturing site, from another site within the same	No, provided that no portion of the batch left direct control of the company for sale or use. It must be clearly visible in the API site's Quality System as a return triggered by the API manufacturing site so this is clear in quality system trend reporting and in the Product Quality Review [ICH Q7, Sections 2.50,

		company be recorded as a 'recall'?	15.13; and 15.14].

16. Contract Manufacturers (including Laboratories)

#	Date of Approval	Questions	Answers
16.1	**June 2015**	Does ICH Q7 preclude a contract manufacturer's independent quality unit from performing the main responsibilities as described in [ICH Q7, Section 2.22]?	No. The original intent of Section 2.2 was to distinguish the main responsibilities (e.g., batch record review, review of non-conformances and investigations, sampling, testing, release or rejection of intermediate or API, etc.) of the independent quality unit from other departments within a company. Contract manufacturers are expected to have an independent quality unit that meet the responsibilities defined in [ICH Q7, Section 2.2] for all activities performed. Given the potential complexity of outsourcing contract manufacturing arrangements, GMP responsibilities should be clearly defined between both parties in detail in a written agreement [ICH Q7, Section 16.12]. However, the overall responsibility for API quality must not be delegated.
16.2	**June 2015**	Which outsourced activities are covered by ICH Q7?	In the context of ICH Q7, contract manufacturing is the outsourced activity. The term 'outsourced activities', as defined and described in [ICH Q10, Section 2.7, Glossary], aligns with the description of 'contract manufacturer' in [ICH Q7, Section 16]. ICH Q7 defines 'manufacture' as '*all operations of receipt of materials, production, packaging, repackaging, labelling, relabeling, quality control, release, storage, and distribution of APIs and related controls*.' 'Related controls' include any activities or services necessary to support production (e.g., maintenance, calibration, etc.). ICH Q7 applies to any activities performed by the original manufacturer or the company that is performing the activity on behalf of the original manufacturer.
16.3	**June 2015**	What is meant by 'where subcontracting is allowed' [ICH Q7, Section 16.14]?	Subcontracting as used in [ICH Q7, Section 16.14] refers to the contract acceptor further contracting out a specific activity to another party (third party). This should only be done when the written and approved contract, as described in [ICH Q7, Section 16.12], specifically allows for such subcontracting. Even when subcontracting is allowed, the original contract giver should approve specific subcontracting before it occurs as stated in [ICH Q7, Section 16.14].

17. Agents, Brokers, Traders, Distributors, Repackers, and Relabellers

#	Date of Approval	Questions	Answers
17.1	**June 2015**	What does ICH Q7 mean by 'Agents, brokers, traders, distributors, repackers, or relabellers'?	Regardless of what they are referred to in different regions, ICH Q7 applies to all parties in the supply chain after the original API/intermediate manufacturer to the drug product manufacturer, in order to maintain the integrity, traceability, and transparency of the supply chain [ICH Q7, Section 17.1].

17.2	**June 2015**	Could a distributor of an API engage a contract manufacturer for production Steps?	No. If a distributor [ICH Q7, Section 17.1] of an API contracts out production Steps (e.g., drying, micronisation, milling, or sieving), then the distributor becomes a manufacturer and is subject to the entirety of ICH Q7. This includes, but is not limited to, appropriate written agreements as stated in [ICH Q7, Section 16.12] defining responsibilities of each party. In addition, these contracted production steps must be described in registration documents, applications, or equivalent as per regional requirements.
17.3	**June 2015**	Is it acceptable to replace the original label, which contains the information of the original manufacturer?	Any relabeling operations are considered manufacturing by definition [ICH Q7, Section 20] and should be performed under appropriate GMP controls [ICH Q7, Section 17.40]. With appropriate justification, manufacturers including repackagers and relabellers may replace the original label. The new label should contain information as per [ICH Q7, Sections 9.42, 9.43]. However, distributors should not remove an original label, but only add additional labels. Information about the original manufacturer must be provided to the customers [ICH Q7, Section 17.61]. Overall, the traceability of the supply chain needs to be maintained [ICH Q7, Section 17.2].
17.4	**June 2015**	Who is considered to be the original manufacturer of the API for purposes of the Certificate of Analysis (CoA)?	The CoA should document the original manufacturer to support traceability throughout the supply chain [ICH Q7, Sections 11.4, 17.6]. The original manufacturer would be the facility where the final purified API/intermediate is produced. Further physical processing (e.g., drying, micronisation, milling, sieving) of an API would not make the manufacturer performing such operations the original manufacturer. All authentic CoAs including those of the original manufacturer should be available [ICH Q7, Section 17.20].

18. Specific guidance for APIs manufactured by cell culture/fermentation

#	Date of Approval	Questions	Answers
18.1	**June 2015**	Does ICH Q7 expect validation for viral removal/viral inactivation steps for biological/biotechnological products?	Yes. According to [ICH Q7, Section 18.51], viral inactivation/removal steps are considered critical for some processes (e.g., cell lines of human and animal origin [ICH Q5A, Section 1]. Parameters for validation should be established in accordance with [ICH Q5A, Q5D and Q6B]. Due to the potential for contamination [ICH Q5A, Section 2.B], viral inactivation studies should be performed in a separate and typically smaller laboratory facility [ICH Q11, Section 7.2] and not in a clinical or commercial manufacturing facility.
18.2	**June 2015**	Do [ICH Q7, Sections 18.14, 18.2] apply to classical fermentation and biotechnology?	For 'classical fermentation', the text from [ICH Q7, Section 18.14] '*…this guide covers cell culture/fermentation from the point at which a vial of the cell bank is retrieved for use in manufacturing*' refers to 'classical fermentation' and not to the 'biotechnology fermentation/cell culture'. Although the entire ICH Q7 Guideline does not apply prior to the introduction of cells into the classical fermentation process, as shown in Table 1 of [ICH Q7, Section 1.3], an appropriate level of GMP controls suitable for cell banks should be established.

			For 'biotechnology fermentation/cell culture' [ICH Q7, Section 18.2] on '*Cell Bank Maintenance and Record Keeping*' applies specifically to biotechnology fermentation/cell culture because ICH Q7 starts with the maintenance of the working cell bank [ICH Q7, Section 1.3, Table 1]. Although for biotech products the entire ICH Q7 Guideline does not apply prior to the maintenance of the working cell bank, an appropriate level of GMP controls suitable for cell banks should be established. See also [ICH Q5B, ICH Q5D].

19. APIs for use in clinical trials

#	Date of Approval	Questions	Answers
19.1	**June 2015**	Is it permitted to use the same equipment to manufacture materials to be used in pre-clinical and clinical trials?	Yes. As long as operations are conducted under GMP conditions according to ICH Q7, including the establishment of effective cleaning methods, safe residue limits and appropriate containment measures [ICH Q7, Section 19.3].

20. Glossary

#	Date of Approval	Questions	Answers
20.1	**June 2015**	Are the terms 'deviation' and 'non-conformance' synonyms?	No. However, they are related. The term 'deviation', as used in ICH Q7, refers to a '*departure from an approved instruction or established standard*' that may or may not have an impact on the quality of the material. '*Non-conformance*' refers to a status as a result of a failure of the material to meet specifications or appropriately established standards that impacts the quality of the material [ICH Q7, Sections 2.50, 14.30, 20].

21. ANNEX: Q&As linked to the respective Sections of ICH Q7

Sections of ICH Q7	1: Introduction	2: Quality Management	3: Personnel	4: Buildings and Facilities	5: Process Equipment	6: Documentation and Records	7: Materials Management	8: Production and In-Process Controls	9: Packaging and Identification Labelling of APIs and Intermediates	10: Storage and Distribution	11: Laboratory Controls	12: Validation	13: Change Control	14: Rejection and Re-use of Materials	15: Complaints and Recalls	16: Contract Manufacturers (including Laboratories)	17: Agents, Brokers, Traders, Distributors, Repackers, and Relabellers	18: Specific Guidance for APIs manufactured by Cell Culture/Fermentation	19: APIs for Use in Clinical Trials	20: Glossary	Other ICH Guidelines
1. Introduction – Scope																					
1	1.3																				Q11 Q5B Q5D
2	1.2																			20	
2. Quality Management																					
1		2.13																			
2		2.13 2.22									11.12 11.10					16.10				20	
3		2.22																			
4		2.22	3.10			6.52					11.12										
5		2.50																			Q10
6		2.50 2.51																			Q9
3. Personnel																					
1			3.12																		
2		2.2	3.3																		Q10
4. Buildings and Facilities – Containment																					
1				4.40 4.41																	E2E Q9
2				4.42																	Q9
5. Process Equipment – Cleaning																					
1					5.23							12.76 12.7									
2					5.21 to 5.25			8.50				12.76									
3					5.21							12.7									
4					5.23			8.50				12.7									
5												12.72to 12.76									
6. Documents and Records																					
1						6.13											17				
2						6.51															
3		2.21 2.3				6.5															
7. Materials Management																					
1							7.20 7.24														
2							7.11 7.12 7.31														Q9
3							7.31														
4							7.11 7.31														
5							7.30 7.32														
6							7.5													20	
8. Production and In-Process Control																					
1						6.41		8.14													
2								8.40 8.41													
9. Packaging and Identification Labelling of APIs and Intermediates																					
10. Storage and Distribution																					

Sections of ICH Q7	1: Introduction	2: Quality Management	3: Personnel	4: Buildings and Facilities	5: Process Equipment	6: Documentation and Records	7: Materials Management	8: Production and In-Process Controls	9: Packaging and Identification Labelling of APIs and Intermediates	10: Storage and Distribution	11: Laboratory Controls	12: Validation	13: Change Control	14: Rejection and Re-use of Materials	15: Complaints and Recalls	16: Contract Manufacturers (including Laboratories)	17: Agents, Brokers, Traders, Distributors, Repackers, and Relabellers	18: Specific Guidance for APIs manufactured by Cell Culture/Fermentation	19: APIs for Use in Clinical Trials	20: Glossary	Other ICH Guidelines
1		2.22								10.20						16.12					
11. Laboratory Controls																					
1											11.2 11.21										Q9 Q11
2											11.51		13.11								Q1A
3											11.6										
4											11.71									20	
5											11.72										
12. Validation																					
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3							7.14					12.1	13.13								
4												12.44									
13. Change Control																					
1													13.17				17.60				
14. Rejection and Re-use of Materials																					
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15. Complaints and Recalls																					
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16. Contract Management (including Laboratories)																					
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17. Agents, Brokers, Traders, Distributors, Repackers, and Relabellers																					
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19. APIs for Use in Clinical Trials																					
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20. Glossary																					
1		2.50												14.30						20	

Q8/Q9/Q10 Questions and answers

For general clarification

	Date of Approval	Questions	Answers
1	June 2009	Is the minimal approach accepted by regulators?	Yes. The minimal approach as defined in Q8(R2) (sometime also called 'baseline' or 'traditional' approach) is the expectation which is to be achieved for a fully acceptable submission. However, the 'enhanced' approach as described in ICH Q8(R2) is encouraged (Ref. Q8(R2) Appendix 1).
2	Oct. 2009	What is an appropriate approach for process validation using ICH Q8, Q9 and Q10?	The objectives of process validation are unchanged when using ICH Q8, Q9 and Q10. The main objective of process validation remains that a process design yields a product meeting its pre-defined quality criteria. ICH Q8, Q9 and Q10 provide a structured way to define product critical quality attributes, design space, the manufacturing process and the control strategy. This information can be used to identify the type and focus of studies to be performed prior to and on initial commercial production batch. As an alternative to the traditional process validation, continuous process verification [see definition in ICH Q8(R2) glossary] can be utilised in process validation protocols for the initial commercial production and for manufacturing process changes for the continual improvement throughout the remainder of the product lifecycle.
3	Oct. 2024	How can information from quality risk management and continuous process verification provide for a robust continual improvement approach under ICH Q8, Q9 and Q10?	Like the product itself, process validation also has a lifecycle (process design, process qualification and ongoing process verification). A risk assessment conducted prior to initial commercial validation batches can highlight the areas where particular focus and data are needed to demonstrate a high level of assurance of commercial process robustness. Continual monitoring (e.g., via Continuous Process Verification) can further demonstrate the actual level of assurance of process consistency and provide the basis for continual improvement of the product. Quality Risk Management methodologies of ICH Q9(R1) can be applied throughout the product lifecycle to maintain a state of process control.

Quality by design topics

Date of Approval		Questions	Answers
1	Oct. 2024	Is it always necessary to have a Design Space (DS) or Real Time Release Testing (RTRT) to implement QbD?	Under Quality by Design, establishing a design space or using RTRT is not necessarily expected [ICH Q8(R2), *Step 4*].

Design space

Date of Approval		Questions	Answers
1	Apr. 2009	Is it necessary to study multivariate interactions of all parameters to develop a design space?	No, the applicant will need to justify the choice of material attributes and parameters for multivariate experimentation based on risk assessment and desired operational flexibility.
2	Oct. 2024	Can a design space be applicable to scale-up?	Yes, when appropriately justified [additional details see Q8(R2) Section 2.4.4].
3	Oct. 2024	Can a design space be applicable to a site change?	Yes, it is possible to justify a site change using a site independent design space based on a demonstrated understanding of the robustness of the process and an in-depth consideration of site-specific factors, e.g., materials, equipment, personnel, utilities, manufacturing environment, and equipment. There are region specific regulatory requirements associated with site changes that need to be followed.
4	Apr. 2009	Can a design space be developed for single and/or multiple-unit operations?	Yes, it is possible to develop a design space for single unit operations or across a series of unit operations [see Q8(R2) Section 2.4.3].

Date of Approval		Questions	Answers
5	Oct. 2024	Is it possible to develop a design space for existing products?	Yes, it is possible. Manufacturing data and process knowledge can be used to support a design space for existing products. Relevant information should be utilised from e.g., commercial scale manufacturing, raw materials, process improvement, CAPAs, development data, and relevant knowledge from risk review. For manufacturing operations run under narrow operational ranges in fixed equipment, an expanded region of operation and an understanding of multi-parameter interactions may not be achievable from existing manufacturing data alone and additional studies may be needed to develop a design space. Sufficient knowledge should be demonstrated, and the design space should be supported experimentally to investigate interactions and establish parameter/attribute ranges.
6	Apr. 2009	Is there a regulatory expectation to develop a design space for an existing product?	No, development of a design space for existing products is not necessary unless the applicant has a specific need and desires to use a design space as a means to achieve a higher degree of product and process understanding. This may increase manufacturing flexibility and/or robustness.
7	Jun. 2009	Can a design space be applicable to formulation?	Yes, it may be possible to develop formulation (not component but rather composition) design space consisting of the ranges of excipient amount and its physicochemical properties (e.g., particle size distribution, substitution degree of polymer) based on an enhanced knowledge over a wider range of material attributes. The applicant should justify the rationale for establishing the design space with respect to quality attributes such as bioequivalence, stability, manufacturing robustness etc. Formulation adjustment within the design space depending on material attributes does not need a submission in a regulatory postapproval change.

	Date of Approval	Questions	Answers
8	Jun. 2009	Does a set of proven acceptable ranges alone constitute a design space?	No, a combination of proven acceptable ranges (PARs) developed from univariate experimentation does not constitute a design space [see Q8(R2), Section 2.4.5.]. Proven acceptable ranges from only univariate experimentation may lack an understanding of interactions between the process parameters and/or material attributes. However proven acceptable ranges continue to be acceptable from the regulatory perspective but are not considered a design space [see ICH Q8(R2) Section 2.4.5]. The applicant may elect to use proven acceptable ranges or designspace for different aspects of the manufacturing process.
9	Oct. 2024	Should the outer limits of the Design Space be evaluated during process validation studies at the commercial scale?	No, there is no need to run the process qualification batches at the outer limits of the design space during process validation studies at commercial scale. The design space must be sufficiently explored earlier during development studies (for scale up see also Chapter 2.1 Design Space Question 2; for life cycle approach see Chapter 1.1 for general clarification Question 3).

Real Time Release Testing (RTRT)

	Date of Approval	Questions	Answers
1	Oct. 2024	How is batch release affected by employing RTRT?	Batch release is the final decision to release the product to the market regardless of whether RTRT or end product testing is employed. End product testing involves performance of specific analytical procedures on a defined sample size of the final product after completion of all processing for a given batch of that product. Results of RTRT are handled in the same manner as end product testing results in the batch release decision. Batch release involves an independent review of batch conformance to predefined criteria through the review of testing results and manufacturing records, together with an effective quality system that ensures GMP compliance, regardless of which approach is used.

Date of Approval	Questions	Answers

2	Apr. 2009	Does RTRT mean elimination of end product testing?	RTRT does not necessarily eliminate all end product testing. For example, an applicant may propose RTRT for some attributes only or not all. If all CQAs (relevant for RTRT) are assured by in-process monitoring of parameters and/or testing of materials, then end product testing might not be needed for batch release. Some product testing will be expected for certain regulatory processes such as stability studies or regional requirements.
3	Apr. 2009	Is a product specification still necessary in the case of RTRT?	Yes, product specifications [see ICH Q6A and Q6B] still need to be establishedand met, when tested.
4	Oct. 2024	When using RTRT, is there a need for stability test methods?	Even where RTRT is applied, a stability monitoring protocol that uses stability-indicating methods is required for all products regardless of the means of release testing. [see ICH Q1A and ICH Q5C].
5	Oct. 2024	What is the relationship between Control Strategy and RTRT?	RTRT, if utilized, is an element of the Control Strategy and may enables appropriate in-process testing (in-line, on-line, at-line) of quality attributes rather than testing on the end product. This use of RTRT recognises that under specific circumstances an appropriate combination of process controls (critical process parameters) together with pre-defined material attributes may provide greater assurance of product quality than end product testing and as such be an integral part of the control strategy.
6	Oct. 2024	Do traditional sampling approaches apply to RTRT?	No, traditionally sampling plans for in-process and end-product testing involve a discrete sample size that represents the minimal sampling expectations. Generally, the use of RTRT will include more extensive on-line/in-line measurement. A scientifically sound sampling approach should be developed, justified, and implemented.
7	Oct. 2024	If RTRT results fail or trending toward failure, can end-product testing be used to release the batch?	No, in principle the RTRT results should be routinely used for the batch release decisions and not be substituted by end-product testing. Any failure should be investigated, and trending should be followed up appropriately. However, batch release decisions will need to be made based on the results of the investigations. The batch release decision needs to comply with the content of the marketing authorisation and GMP compliance.

Date of Approval	Questions	Answers

8	Oct. 2024	What is the relationship between in-process testing and RTRT?	In-process testing includes any testing that occurs during the manufacturing process of drug substance and/or finished product. RTRT includes those in-process tests that directly impact the decision for batch release through evaluation of Critical Quality Attributes.
9	Jun. 2009	What is the difference between 'real time release' and 'RTRT'?	The definition of RTRT in Q8(R2) is 'the ability to evaluate and ensure the acceptable quality of in- process and/or final product based on process data, which typically includes a valid combination of measured material attributes and process controls. The term 'Real time release' in the Q8(R2), *Step 2* document was revised to RTRT in the final Q8(R2) Part II document to fit the definition more accurately and thus avoid confusion with batch release.
10	Oct. 2024	Can a surrogate measurement be used for RTRT?	Yes, RTRT can be based on measurement of surrogate (e.g., process parameter, material attribute) that has been demonstrated to correlate with an in-process or end-product specification [see ICH Q8(R2); Section 2.5.].
11	Oct. 2024	What is the relationship between RTRT and Parametric Release?	Parametric release is one type of RTRT. Parametric release is based on process data (e.g., temperature, pressure, time for terminal sterilization, physicochemical indicator) rather than the testing of material and/or a sample for a specific attribute.

Control Strategy

Refer to the definition of control strategy provided in the ICH Q10 glossary: Q10 Control Strategy definition: 'a planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

	Date of Approval	Questions	Answers
1	Apr. 2009	What is the difference in a control strategy for products developed using the minimal approach vs. 'quality-by-design' approach?	Control strategies are expected irrespective of the development approach. Control strategy includes different types of control proposed by the applicant to assure product quality (Section 3.2.1 ICH Q10), such as in-process testing and end-product testing. For products developed following the minimal approach, the control strategy is usually derived empirically and typically relies more on discrete sampling and end product testing. Under QbD, the control strategy is derived using a systematic science and risk-based approach. Testing, monitoring or controlling is often shifted earlier into the process and conducted in-line, on-line or at-line testing.
2	Apr. 2009	Are GMP requirements different for batch release under QbD?	No, the same GMP requirements apply for batch release under minimal and QbD approaches.
3	Apr. 2009	What is the relationship between a Design Space and a Control Strategy?	A control strategy is required for all products. If a Design Space is developed and approved, the Control Strategy [see ICH Q8(R2), Part II, Section 4] provides the mechanism to ensure that the manufacturing process is maintained within the boundaries described by the Design Space.
4	Jun. 2009	What approaches can be taken in the event of on-line/in- line/at-line testing or monitoring equipment breakdown?	The control strategy provided in the application should include a proposal for use of alternative testing or monitoring approaches in cases of equipment failure. The alternative approach could involve use of end product testing or other options, while maintaining an acceptable level of quality. Testing or monitoring equipment breakdown needs to be managed in the context of a deviation under the Quality System and can be covered by GMP inspection.
5	Oct. 2009	Are product specifications different for minimal versus QbD approaches?	In principle, no, the same product specifications are needed for minimal and QbD approaches. For a QbD approach, the control strategy may allow achieving the end product specifications via RTRT approaches [see ICH Q8(R2), Appendix 1]. Product must meet specification, when tested.

Pharmaceutical Quality System

Date of Approval	Questions	Answers
1 Oct. 2024	What are the benefits of implementing a Pharmaceutical Quality System (in accordance with ICH Q10)?	The benefits are: • A robust manufacturing process, through facilitation of continual improvement through science and risk-based post approval change processes; • Consistency in the global pharmaceutical environment across regions; • Transparency of systems, processes, organizational and management responsibility within, and across, companies (e.g., contract organizations); • Clearer understanding of the application of the Pharmaceutical Quality System throughout product lifecycle; • Further reduced risk of product failure and incidence of complaints and recalls, thereby providing greater assurance of pharmaceutical product consistency and availability (supply) to the patient; • Better process performance, supported by effective risk reviews; • Opportunities to increase understanding between industry and regulators and more optimal use of industry and regulatory resources. Enhanced manufacturer's and regulators' confidence in product quality; • Greater assurance of compliance with GMP, which builds confidence in the regulators and which may result in shorter inspections. • Knowledge-driven and objective risk assessments which help achieve science- and risk-based control strategies, and which lead to effective risk-based decisions as well as reduced product availability risks relating to quality/manufacturing issues.

Date of Approval		Questions	Answers
2	Apr. 2009	How does a company demonstrate implementation of PQS in accordance with ICH Q10?	When implemented, a company will demonstrate the use of an effective PQS through its documentation (e.g., policies, standards), its processes, its training/qualification its management its continual improvement efforts, and its performance against pre-defined Key Performance Indicators [see ICH Q10 glossary on 'Performance indicator']. A mechanism should be established to demonstrate at a site how the PQS operates across the product lifecycle, in an easily understandable way for management, staff and regulatory inspectors, e.g., a quality manual, documentation, flowcharts, procedures. Companies can implement a program in which the PQS is routinely audited in-house (i.e., internal audit program) to ensure that the system is functioning at a high level.
3	Oct. 2024	Is it necessary to describe the PQS in a regulatory submission?	No, however relevant elements of the PQS, such as quality monitoring system, change management, and deviation management may be referenced as part of the control strategy as supporting information.
4	Oct. 2024	Is there certification that the PQS is in accordance with ICH Q10?	No. There is no specific ICH Q10 certification programme.
5	Apr. 2009	How should the implementation of the design space be evaluated during inspection of the manufacturing site?	Inspection should verify/assess that manufacturing operations are appropriately carried out within the Design Space. The inspector in collaboration with the assessor, where appropriate, should also verify successful manufacturing operations under the Design Space and that movement within the Design Space is managed within the company's change system [see ICH Q10, Section 3.2. Table III].
6	Apr. 2009	What should be done if manufacturing operations run inadvertently outside of the Design Space?	This should be handled as a deviation under GMP. For example unplanned 'one-off 'excursions occurring as a result of unexpected events, such as operator error or equipment failure, would be investigated, documented and dealt with as a deviation in the usual way. The results of the investigation may contribute to the process knowledge, preventive actions and continual improvement of the product.

Date of Approval		Questions	Answers
7	Oct. 2024	What information and documentation of the development studies should be available at a manufacturing site?	Pharmaceutical development information (e.g., supporting information on design space, chemometric model, outputs of quality risk management activities,…) is available at the development site. Pharmaceutical development information which is useful to ensure the understanding of the basis for the manufacturing process and control strategy, including the rationale for selection of critical process parameters and critical quality attributes should be available at the manufacturing site. Scientific collaboration and knowledge sharing between pharmaceutical development and manufacturing is essential to ensure the successful transfer to production.
8	Jun. 2009	Can process parameters be adjusted throughout the product lifecycle?	Process parameters are studied and selected during pharmaceutical development and monitored during commercial manufacturing. Knowledge gained could be utilized for adjustment of the parameters as part of continual improvement of the process throughout the lifecycle of the drug product (see ICH Q10, Section 3.).

ICH Quality guidelines' impact on GMP inspection practices

Date of Approval		Questions	Answers
1	Oct. 2024	How do product-related inspections differ in an ICH Q8, Q9 and Q10 environment?	In the case of product-related inspection (in particular pre-authorisation) depending on the complexity of the product and/or process, there may be a need for greater collaboration between inspectors and assessors for example for the assessment of development data. The inspection would normally occur at the proposed commercial manufacturing site and there may be greater focus on enhanced process understanding and understanding relationships e.g., Critical Quality Attribute (CQAs), Critical Process Parameters (CPPs). It may also extend into the application and implementation of quality risk management principles, as supported by the Pharmaceutical Quality System (PQS).

	Date of Approval	Questions	Answers
2	Oct. 2024	How do system-related inspections differ in an ICH Q8, Q9 and Q10 environment?	Such inspections have greater focus (but not only) on how the PQS facilitates the use of e.g., Quality Risk Management methods, implementation of design space and change management [see ICH Q10].
3	Oct. 2024	How is control strategy approved in the application and evaluated during inspection?	Elements of the control strategy submitted in the application are reviewed and approved by the regulatory agency. However, additional elements are subject to inspection (as described in Q10).

Knowledge management

	Date of Approval	Questions	Answers
1	Oct. 2024	How has the implementation of ICH Q8, Q9, and Q10 changed the significance and use of knowledge management?	Q10 defines knowledge management as: 'Systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes and components'. Knowledge Management is not a new concept. It is always important regardless of the development approach. Q10 highlights knowledge management because it is expected that more complex information generated by appropriate approaches (e.g., QbD, PAT, real-time data generation and control monitoring systems) need to be captured, managed and shared during product life-cycle. In conjunction with Quality Risk Management, Knowledge Management can facilitate the use of concepts such as prior knowledge (including from other similar products), development of design space, control strategy, technology transfer, and continual improvement across the product life cycle.
2	April 2009	Does Q10 suggest an ideal way to manage knowledge?	No. Q10 provides a framework and does not prescribe how to implement knowledge management. Each company decides how to manage knowledge, including the depth and extent of information assessment based on their specific needs.

Date of Approval	Questions	Answers
3 Oct. 2024	What are examples of sources of information for Knowledge Management?	Some examples of knowledge sources are: • Prior knowledge based on experience obtained from similar processes (internal knowledge, industry scientific and technical publications) and published information (external knowledge: literature and peer-reviewed publications); • Pharmaceutical development studies; • Mechanism of action; • Structure/function relationships; • Technology transfer activities; • Process validation studies; • Manufacturing experience e.g.: - Internal and vendor audits; - Raw material testing data; • Innovation; • Continual improvement; • Change management activities; • Stability reports; • Product Quality Reviews/Annual Product Reviews; • Complaint Reports; • Adverse event reports (Patient safety); • Deviation Reports, Recall Information; • Technical investigations and/or CAPA reports; • Suppliers and Contractors; • Product history and /or manufacturing history; • Ongoing manufacturing processes information (e.g., trends); • Risk assessments and other quality risk management activities. Information from the above can be sourced and shared across a site or company, between companies and suppliers/contractors, products and across different disciplines (e.g., development, manufacturing, engineering, quality units).

Date of Approval		Questions	Answers
4	Apr. 2009	Is a specific dedicated computerized information management system required for the implementation of knowledge management with respect to ICH Q8, Q9 and Q10?	No, but such computerised information management systems can be invaluable in capturing, managing, assessing and sharing complex data and information.
5	Oct. 2024	Do regulatory agencies expect to see a formal knowledge management approach during inspections?	No. There is no regulatory requirement for a formal knowledge management system. However, it is expected that knowledge from different processes and systems is appropriately utilised. Note: 'formal' in this context means a structured approach using a recognised methodology or (IT-) tool, executing and documenting something in a transparent and detailed manner.

Software solutions

Date of Approval		Questions	Answers
1	Oct. 2024	Is it necessary for a pharmaceutical firm to purchase products that are marketed as 'ICH compliant solutions' or ICH Q8, 9 & 10 Implementation software, etc.to achieve a successful implementation of these ICH guidelines within their companies?	No. ICH has not endorsed any commercial products and does not intend to do so. ICH is not a regulatory agency with reviewing authority and thus does not have a role in determining or defining 'ICH compliance' for any commercial products. If considering such products, firms will need to carry out their own evaluation of these products relative to their business needs. Computer system validation studies should be performed by companies to evaluate the reliability of potential software.

6. ECA Academy

6.1 Questions and Answers on Visual Inspections

ECA Visual Inspection Interest Group, Q&A Document 2.0
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Manual Inspection

MI1 According to Annex 1 of the EU-GMP-Guideline, operators doing the inspection for particles and other defects should make frequent breaks from inspection. Are there any regulations concerning rest times and time intervals?
An interpretation of this requirement is not trivial. Sometimes, the companies interpret it in a significantly different way. In practice, for example, the following variants can be found:
55 minutes inspecting, 5 minutes break over a period of 8 hours
20 minutes inspecting, 20 minutes other activities over a period of 8 hours
20 minutes inspecting, 5 minutes break over a period of 4 hours

It is a known fact that this activity normally can be carried out successfully for a maximum period of 15 to 20 minutes. Insofar the provision "55 minutes inspecting, 5 minutes break over a period of 8 hours" doesn't seem to be appropriate. Ideally, the activity of inspection will be limited to 15 to 20 minutes. Afterwards a break for the eyes should be taken without carrying out any other activities.

MI2 Which requirements should there be concerning the requalification of the personnel carrying out the optical inspection? Are there specific time intervals to be observed and should the requalification be announced?
The pharmaceutical companies have different approaches concerning the time intervals for requalification. The intervals reach from each month to every two years. Every two years certainly is too long. This period of time is especially problematic if the person carrying out the inspections doesn't pass the requalification any more. Which consequences does this have for the batches inspected by this operator? Insofar it seems to be appropriate to choose a time interval that is as short as possible and to control the personnel for example by means of an AQL testing. Are test sets used in the context of the requalification this should not be announced before the qualification run. For this reason, it is advisable to requalify not exactly every six/twelve months, for example, but to do this on a random basis i.e. to lay down irregular time intervals. If test kits are processed in the context of requalification you need to think carefully about the question whether the test kits should be inspected directly in the morning or at the end of the day in the case of an eight-hour shift. Naturally, it is advisable to choose the worst case situation and therefore, to let the inspection be carried out at the end of the shift.

MI3 How often have employees of the manual (or semi-automatic) inspection to be trained? What does "regularly" mean in this context?
With regard to visual inspection, the difference between initial qualification and requalification must basically be made. Strictly speaking, requalification is an examination of the status of a person's qualification. It is recommended to re-qualify employees at least every 12 months.

MI4 Should the set of samples for the qualification (training) of the staff be taken directly form the production rejects or should it be produced artificially based on typical defects?
Usually, the training set should be taken directly from the production rejects. Unfortunately, some failures occur only very rarely so that you have to produce some of them yourself. Finally, you have a set with failures that are typical for the production that has to undergo a formal release procedure described in an SOP. This guarantees that the failures are typical and that you can use them for training.

MI5 Are there empirical values about how long do lamps in semi-automatic testing stations keep their intensity?

Here, the certificates of the lamp manufacturers should be consulted. Usually, 2-3 years are indicated. In many companies, the lamps are exchanged routinely after one year to never have to question the test results due to possible lamp weakness retrospectively.

MI6 We have trained our inspection team to inspect containers in less than 5 seconds against a white and black background. Moreover we do an AQL testing afterwards and if the AQL fails the qualification status of the inspector will also be evaluated within a deviation. So is it allowed so shorten the inspection time?
Ph.Eur. and USP requirements for particulates are clear – manual visual inspection for 5 sec in front of black and white background is required. Annex 1* of the GMP guidance document states to use a given time and given set-up for inspection. Any modification must be validated and should show to be equal or better than the compendial approach.
*(Vs. 2008 rev.)

MI7 According to Ph.Eur the light intensity should be between 2000-3750 Lux but according to USP 790 it should be minimum 2000-3750 Lux. Is it ok then that the light intensity is higher than 3750 Lux?
The "minimum intensity" in USP <790> refers to 2000 Lux. But higher intensities as 3750 Lux or higher are possible and acceptable for certain types of products (e.g. Blow-Fill-Seal container). But operators fatigue will be higher and you have to adopt the eye breaks and the inspection time per day accordingly.

MI8 Is the wearing of anti reflective eyewear by manual inspectors a common practice among pharmaceutical companies during Manual or Semi automatic inspection as a measure against fatigue?
Wearing anti reflective eyewear is not the way for improving the quality of the visual inspection. On one hand a high light intensity can be necessary, on the other hand the tiring of the human eye seems to work contra productive to the detecting of the defects. One has to find a way between both effects meaning: use more eye breaks when using light with a higher intensity.

MI9 Is there a requirement in regards to the size of the visual inspection booth, e.g. width, length, etc?
No

MI10 How can foreign particulate matter be distinguished from a micro bubble in a vial that can form during vial stirring during manual inspection?
Up to now there are limited technologies for distinguishing air bubbles and real particles. Cameras and the human eye cannot see a difference when the particles/air bubbles are small. The only way is to avoid air bubbles. One approach is the use of two cameras. In case particle camera1 detects something but particle-camera2 (under the same conditions as camera1) does not, it is likely an air bubble.

MI11 What exactly is meant by point 2.1 of the best practice paper ("The relative humidity and air velocity should be controlled and ensure comfortable working conditions.")? Is a permanent room monitoring required?
It is a fundamental GMP requirement: the fulfilment of a requirement has to documented. A permanent monitoring of temperature and humidity may not be necessary, but how to prove during an inspection, that the working conditions for the human inspectors have been adequate? This will not be possible without measuring temperature and humidity and some sort of system, meaning the documentation and evaluation of measuring data. If this is not part of the building control system anyway, a manual system may also be possible.

Automated Inspection

AV1 The grey portion of fully automatic control is often checked manually, to return not clearly or fully tested products back to the inspection process. Is it allowed to carry out this testing with the automated inspection machine?

From a GMP view, there are no restrictions. It is also important here that at the end a yield calculation and evaluation in the batch record appears. And there are also automated inspection systems that have already integrated the double inspection with multiple cameras.

AV2 Can one reject test be considered as a good after two "good" inspection on the same machine?
This is possible in a few cases where - for example - the machine stopped and goods were therefore ejected. Otherwise, "reject" should always remain "reject". This is particularly applicable to "bad" goods which have been rejected because of particles or opacity. Containers sorted out due to cosmetic defects are however usually being re-inspected

AV3 We produce a lot of products with different formats. Until now we use a rejection rate of <2% as acceptance criterion and sets of samples from production to control the functionality of the machine.
An AQL test should be carried out for each batch. In the meantime this is expected by the authorities and inspectors. This is also described in the ECA Good Practice Guide on Visual Inspection. A control of the rejection rate of the 100% inspection is also expected but it rather serves for recognizing whether a batch differs from the normal unobtrusive production. This trending limits should be product specific. A generic limit eg <2% would need a rationale.

AV 4 In highly automated manufacturing lines for LVP flexible containers, the visual inspection process may/cannot comply to the standard visual inspection criteria e.g.: 5 sec inspection time, agitation of the container etc. Is this a compliance problem?
The requirements like 5 sec inspection time required by pharmacopoeias are addressing manually performed visual inspection. If the visual inspection is performed automatically, it is the company's responsibility to ensure that the inspection via camera systems is as effective as a manual visual inspection via a validation (e.g. Knapp Test).

AV 5 Do we have to perform challenge test before production / shift to check the 100% automatic visual inspection? And how often?
A function test kit (system suitability test kit) used before and after the inspection of each batch to demonstrate the functionality of the fully automated inspection system. It may contain an abridged set of more apparent defects such as big particles, cracked or empty containers.

Qualification /Validation

QV1 In the course of validation and during operation there are recurring problems with false reject rates in the case of fully automated systems. Are there any GMP requirements concerning this?
Due to the fact that the systems are able to detect also considerably smaller particles than human operators there are repeatedly emerging more or less big amounts of objects in the part with defects that have been assessed by a human operator as being good. Furthermore, a fully automated system might also get problems with air bubbles and reject these objects as having defects. In the end, the trick is to configure the system in such a way that no objects containing very small particles are rejected. In some companies the objects rejected by automated systems are again inspected by human operators. But this method entails the risk that objects actually having defects are suddenly classified as having no defects by the human operator. Two conclusions can be drawn from the point of view of GMP. Rejecting objects without defect does not entail a risk for patients and thus seems to be practicable. On the other hand one could also criticise the qualification as such since a system making errors is not sufficiently qualified. In any case, acceptance criteria should be defined for the part with defects. In the case of exceedance certain measures are to be taken such as an additional 100 % inspection for example. To sum it up: there is no requirement to set a limit for false rejects. But on the other hand it is advisable to also set a limit for the false rejects, usually during the qualification/5000 test. Because having no limit or a very high number of false rejects may question the whole qualification during a GMP inspection.

QV2 We have about 50 different aqueous solutions for a few hundred products (one solution for several formats). So far we have prepared one set of samples (function set,

qualification set including Knapp set) from production rejects. This is very time-consuming. Do you think it might be useful to measure parameters such as viscosity, surface tension of the 50 solutions in order to group the products (bracketing)?
Bracketing is useful here. The rationale using viscosity is ok.

QV3 Which statistical tests should be applied to demonstrate equivalence of different visual inspection processes (e.g. manual versus automatic inspection process)?
The goal of the AIM qualification is to show that the machine is equal or better than the "gold standard" that is the human inspection. This can be done by comparing the overall detection rates for particles (this set also includes non-particle objects) and at least 10 inspections runs of this set for manual inspection (normally 3 operators) and the same set of objects on the machine. For non-particle defects (scratches, missing stopper,…) one could use a predefined limit or also a man/machine comparison.

Test Sets

TS1 What are the differences between qualification, particle (Knapp test) and function test set?
The function test set serves for a sort of system suitability test, i.e. this test is used to test before and after each batch whether the cameras are functioning correctly. Usually, no challenging samples are used for this, but rather unities with particles having a detection rate of 100% such as particles with a size of 1000 µm, vials with missing stoppers.

Qualification test set: the qualification test set consists of product specific containers containing the product and having all known "static" defects (scratches, wrong flip-off, missing stopper,...). Usually, about 10-20% of the containers of the set have a defect. New failures or defects are added to the qualification test set.

Particle test set (Knapp-Test): Sets that contain only particles. These are particles having the size from 50µm to 1000µm and consisting of different materials (plastic, the material stoppers are made of, glass, metal). Hence, they are "non-static", i.e. the defect is in the container or in the drug solution. Particle test sets are part of the qualification test set at the same time.

TS2 Should all these test sets be prepared artificially? Should this be done, for instance, by an external laboratory with defined failures?
We prepare the static defects in-house and a part of the non-static defects (particle defects) are produced externally. But it is also possible to have everything produced externally. But the static defects should be the same that are generated in the worst case by your production machines. Therefore, I advise to make these in-house and get the release from QA. In this way you would have representative bad samples from your process. In the best case you take bad samples from your process but it is not possible to do this for all samples

TS3 The problem is that sets of samples have to be remade regularly since they have expired. How do you prepare the function test set?
Usually, our sets keep several years. Single samples have to be replaced again and again. These single samples are then released by QA and we introduce them into the set. The sets should be controlled at least once a year and be released again afterwards.

TS4 How long can a training kit be used?
Training kits should contain all kind of defects and must be updated constantly with new evolving defects out of production. Expiry of specific defects depends on nature (a crack will not expire; small particles may clot together…). The set must be regularly released and reinspected by a supervisor.

TS5 How should qualification sets be prepared for a new product?
All representative defects coming from a production line should be included in the set. Some of the defects need to be generated but if possible should be taken from production. These defects need to be classified. See chapter 5 of the Best Practice Guide.

Requalification

RQ1 If systems for the fully automatic visual inspection are used, regular functional testing is carried out. Must the system be requalified nevertheless?

According to EU-GMP a difference must be made between the following activities in the case of a fully automated system:

- Qualification: in the case of new equipment
- Requalification: Assessment of equipment within defined time intervals
- Functional testing: Test carried out before start of work (and preferably also after work)
- Periodic evaluation: According to EU-GMP Annex 11.

Functional testing addresses the sensor functionality only and is typically carried out before and after batch inspection. Due to its limited scope, functional testing cannot replace requalification of an equipment. Requalification should be performed according to the EU-GMP Annex 15 to safeguard that the whole equipment remains in a state of control. Requalification programs and intervals shall be planned and justified according to the guideline. In the context of the assessment of the facility, the functional testing carried out until the date of requalification will certainly be part of the assessment.

RQ2 Requalification: If the regular requalification of the automatic inspection machine is carried out by means of the test of 5,000 does this mean that the 5,000 vials from one production batch must all be controlled manually and by the automatic inspection machine?

I.e. is it necessary to repeat the man-machine-comparison that was carried out in PQ? Almost correct. PQ consists of the particle (Knapp test) run, the run concerning the "static" defects and also of a run of 5,000 of GOOD vials. This run of 5,000 is carried out once a year for each product. The Knapp test and the "static" test are not repeated except when there have been changes at the particle detection stations. Without changes (something that occurs only very seldom) only the test of 5,000 is carried out, i.e. 5,000 vials from the automatic inspection machine are inspected by a person and by the machine

AQL-Testing

AQ1 Is AQL testing mandatory as a part of the visual inspection?

A direct requirement cannot be derived from the EU GMP. Yet, the AQL tests correspond to the state of the art in science and technology. Since we know that neither a manual nor an automated visual inspection can guarantee a 100% particle-free batch, an additional measure - like the AQL tests - is certainly appropriate. Another method would be of course a second 100% inspection. Or you could show in the validation that the test method used is a 100% flawless and complete, what will hardly be possible in practice. For US, the AQL testing has been included in the USP, chapter <790>.

AQ2 Do the European agencies follow the rules for AQL testing given in USP <790>?

There is no written guidance in Europe requiring an AQL test according USP <790>. Companies have to define their own way to implement a check of the visual inspection efficacy.

AQ3 Should the AQL be inspected by QC or production

AQL manual inspection may be carried out by production staff (to avoid setting up a separate visual inspection team in QC) under a quality oversight or the quality unit. If performed by production operators, the AQL test should not be done by members of the team that was performing the 100 % visual inspection of the batch.

AQ4 Is the AQL acceptance criteria of 0.65 for the particles only or for the overall defects?

USP <790> addresses visual inspection for particles. So the requirement to apply an AQL of 0.65 or sample plans with better protection applies to particles. Other defects like cracks or stopper failures may be addressed with tighter AQLs.

AQ5 Which sample size should be taken if various AQL-levels depending on the defect criticality are used (for example batch size of 22.000, AQL = 0 for critical defects, AQL = 0.65 for major defects, AQL = 2.0 for minor defects)

There is a misunderstanding. The sample size is depending on the Quality Level one wants to use (e.g. level II). With this level and the batch size one gets the size of the sample which must be drawn. The AQL level (e.g. 0.65) then defines how many defects are allowed to accept the defined batch quality. Of course the AQL level then depends on the criticality because the more critical the less defects are allowed to be found in the AQL procedure.

AQ6 For vials packaged in separated sub-batches, when the 100% visual inspection is located at the beginning of the packaging process, should the acceptance sampling be statistically significant on the full manufacturing batch or on each single sub-batch?
The AQL sampling should be based on the sub-batch meaning the batch size that is inspected. One is checking with this test if the incoming quality of the batch is according the quality which is expected. The levels do not need to be the same like for the initial batch.

Defect Categorisation

DC1 The USP in sections 790 and 1790 classifies glass defects as a major defect. There are many types of glass defects, e.g. glass particulates adhered to the side of the vial, and loose glass within a vial (in both incidents if product integrity/sterility assurance is not compromised), could you please tell me what the defect classification levels (critical, major or minor), for either of the former mentioned defects should be.

Both USP chapters do not make any classification of defects. This needs to be done by the pharmaceutical company and has to be based on a quality risk assessment

DC2 How should freeze-drying defects such as collapse and melt-back be classified regarding to their criticality
In the scientific literature a melt-back is seen to be critical. The difference of a collapsed and a melt back is difficult to define. A collapsed lyo cake could also be a melt back. One would need to explain this difference and its criticality.

Special Products

SP1 Our DP is a powder. Is visual inspection of the reconstituted solution sufficient?
100% visual inspection of the delivered DP is a general requirement. The inspection of the reconstituted solution would be part of the release process. According USP<1790> special sampling plans according S-3 and S-4 (ANSI/AQS Z1.4) should be used.

SP2 How should the operators performing the supplemental testing be qualified?

Supplemented testing is performed on reconstituted vials and thus has to be performed in a lab environment. The reconstituted vials are tested either by manufacturing operators or QC staff based on the same criteria as training for 100 % visual inspection or AQL testing.

SP3 What is the recommendation for AQL setting for the testing of samples after reconstitution?
This depends on the nature of the product. Taking 0.65 will in many cases disqualify nearly all batches. In some cases it might be an option to allow a second level testing to avoid that 1 single particle in one vial out of 20 requires rejection of your batch.

Regulatory Affairs

RA1 If the 100% visual inspection is followed by an AQL testing, do we have to perform also an test on visual particles at the release (testing) of the batch?
The AQL testing is intended to replace testing for visible particles at release testing in the lab. However, if this test is part of your filing, this has to be done. Or you have to file a variation.

RA2 Is the carrying out of a 100% inspection of parenterals to be understood as IPC testing or as final product testing? Is it possible to carry it out under the responsibility of production or must it be done by QC?
Assigning the activity of a 100% inspection is not trivial at first sight. Formally, this activity is allocated to production. By the way, this is also FDA's point of view. Hence, it also is an activity which requires a manufacturing authorisation within the meaning of § 13 German Medicine Act (AMG). Due to the fact that it is a 100% inspection, it is neither a real IPC nor a final inspection on a random basis. The 100% inspection being attributed to production, it is carried out under the responsibility of the head of production

RA3 Are there legal acceptance criteria or provisions regarding the size of (visible) particles?
According to studies by Jules Knapp, people can recognise particles under optimal conditions from 30 - 50 µm, taking into account the colour of the particle. Other studies have shown that eventually particles from approximately 200 µm can be surely detected - in other sources, values of 50-80 µm can be found. There are (still) no statutory limits on the size of the visible particles

RA4 What does essentially free from particles mean with respect to the US and EU pharmacopeia? Is there a difference?
Up to now there is no official statement from the EMA about the interpretation of "essentially free from particles".

RA5 How has the limit for inherent particles to be set in a registration of a new protein product which is known to form particles?
The guidance according USP<1790> would be to define a limit and to monitor this limit. Of Course this limit needs then to be described within the dossier of the DP.

Process Control / SPC

PC1 How can Process Control Limits in the Visual inspection process be defined?
Typical limits for product and production line need to be established. Therefore see chapter 6 of the Best-Practice Paper. This follows the ASTM E2587-2 standard (Standard Practice for Use of Control Charts in Statistical Process Control).

6.2 Questions and Answers on Good Distribution Practices (GDP)

1. GDP Training

Question 1.1:
What is seen as regular training in GDP; once per two years or a shorter timeframe?
Answer: Regulators expect annual GDP refreshed training for staff. It is up to the company to define how this is achieved and be able to justify their approach. Staff should demonstrate competence for the tasks they perform and the responsibilities they hold. The training frequencies could for example be determined by the complexity of the task and the experience of the staff.

Question 1.2:
How should I review the training effectiveness? Qualitatively or quantitatively? Or by any other means?
Answer: Staff should demonstrate competence for the task performed and for the responsibilities they hold. Review will therefore depend on the subject of the training, all of these are relevant, some training needs formal assessment, others may require observing the trainee to ensure he is capable of performing the task. This should be defined in your training programme, records should be kept.

Question 1.3:
There are different types of wholesalers; for wholesalers with a warehouse it is clear that more training is needed per year. However, a commercial affiliate or trading entity only buys and sells the goods and outsources the warehouse and transport.
Answer: Training should be relevant to the nature of the business, so for a commercial company you need to decide what activities your company is performing, then decide on the nature of training. For example, key focus areas for training would be customer qualification, supplier verification, management of outsourced partners and associated activities. The RP would still retain responsibility for decisions on stock disposition in the event of a complaint, return, recall, suspected falsified medicine etc. as well as documenting physical and financial product flows, generating quality and risk management reports. Finance personnel need to be trained in supporting product recall activities and stock reconciliation. IT systems need to be assessed to demonstrate compliance to GDP and the requirements of data integrity maintained, e.g. effective management of master data.

Question 1.4:
The Responsible Person (RP) should ensure a training programme is in place and staff is trained. Can the training tasks be designated to the human resource department or should this be a part of the QA department?
Answer: We would expect the training is developed and approved by the RP/QA department, in some companies the HR manages and organizes the training sessions.

Question 1.5:
What would be the preferred content of qualification of the GDP trainer?
Answer: Qualified and experienced in GDP.

Question 1.6:
What industry-standard training courses/certification are there for RPs that you can recommend?
Answer: ECA runs courses.

Question 1.7:
Activities to third parties - Are 3 to 5 GDP-related training courses per year then still needed?
Answer: Training should be relevant to the nature of the business, so for a commercial company you need to decide what activities your company is performing, then decide on the nature of training. Regardless of the size or activities of the wholesaler, all personnel need to be trained on the activities being conducted by them including retraining on any updated procedures and annual GDP training. This means that personnel need to be trained on the activities prior to conducting those activities, and so this would not likely be complied with by conducting training at a set frequency as per the question.

Question 1.8:
Are there requirements on training records for specific tasks (handling of deviations, change requests, complaints, release of product etc)?
Answer: Personnel must be trained in the activities being performed by them. Furthermore, personnel should be trained in GDP activities which they may be exposed to - for example: complaints, recalls, falsified medicinal products.

Question 1.9:
What are some examples of how to conduct the periodical assessment of the effectiveness of training?
Answer: Observation of the person conducting the task, discussion of task and related activities with the person, review of previous deviations and complaints, retraining.

Question 1.10:
Regarding training effectiveness: is a knowledge check mandatory?
Answer: Individual training event knowledge checks are not mandatory but is considered best practice. This is also dependent on the type of training being provided. The GDPs do require that the effectiveness of training is routinely evaluated and documented.

Question 1.11:
Is it enough with a training plan for the QA team or does it need to be per employee?
Answer: All employees should have a training plan as it is best practice regardless of whether they are performing GDP activities or not. Furthermore, GDP activities are not usually restricted to the QA team - with, for example operations, sales, warehousing etc being involved as well.

2. The Role of the Responsible Person for GDP

Question 2.1:
Can the Responsible Person (RP) delegate all type of tasks? What about even more critical tasks such as release of product etc.?
Answer: Provided the RP ensures that all delegated tasks are properly documented and described in a formal procedure and the person performing the task has been appropriately trained he/she can delegate the performance of the task. However, the responsibility for that task remains with the RP.

Question 2.2:
What legally-binding documents would the RP need to sign related to the products, besides Quality Agreements?
Answer: Apart from quality related document, no other requirement, but a company may choose to have their RP to sign of various documents.

Question 2.3:
What is the impact of Brexit on RP requirements?
Answer: In UK, companies importing products fro approved countries need to have a Responsible Person (import) (RPi), otherwise there is no change to the role of RP in EU.

Question 2.4:
Can QMR be RP or separate person to be appointed? Also company is doing warehousing and distribution and it has multiple sites (e.g. 14 warehouse in the country in different location), does it require to have RP for all sites?
Answer: RP is a specific role for WDA holders. QMR is a defined role for companies handling APIs. If your company has 14 sites across the country it is unreasonable to assume one RP can manage all these sites, therefore a RP in each site may be required depending on the nature of the company as well as the scope of the licensed activities. They may report to a centrally appointed RP for consistency and management purposes.

Question 2.5:

Which entities need an RP?
Answer: All WDA holders must have an RP.

Question 2.6:
Can the provisions between RP and Deputy RP be described in the Site Master File?
Answer: Yes.

Question 2.7:
Concerning annual training review of non-operation staff performing GDP tasks: is it mandatory that the RP review, document and sign this review or can it be delegated to QA personnel?
Answer: The RP is responsible for ensuring that initial and continuous training programmes are implemented and maintained. How they conduct this is possible through a number of different means and does not always mean that they must sign individual reviews. A review of the entire process may be conducted through, for example self inspection.

Question 2.8:
In your experience, is there a background/profile that tends to be conducive for being successful in the role of RP - e.g. QP experience, people with logistics background, etc.
Answer: This will depend on the nature of the company and the activities being performed. In general, the RP should have experience performing similar activities to the company in question. A broad base of experience is useful as RP's tend to come across issues across the entire supply chain/life-cycle of the product. The best approach (whilst not always practical or possible) may be for the old RP and new RP to have a handover period or for the new RP to have been employed by the company for a period of time prior to taking on the role to ensure they are familiar with the products being wholesaled and operations conducted.

Question 2.9:
For the RP role & ongoing competency assessment, which function is best placed to oversee this: HR, Head of QA, Business Leader, ...?
Answer: The RP themselves are often well-placed to know areas where ongoing professional competence and training is required. Assessment of this may be performed and reviewed by HR or the RP's manager. The RP's manager should understand the RP's role and ensure suitable training is provided.

Question 2.10:
If we are the contract manufacturer + 3PL for legal manufacturer/legal distributor who should have RP employee under organization chart?
Answer: The holder of the WDA is required to have the services of a RP. If this RP is not an employee of the legal entity being the WDA holder, then a contract should be in place between the RP employer and the WDA holder as the RP would be considered a contract RP. This contract should set out the availability of the RP to the WDA holder including the number of days per month etc.

3. Quality Management System (QMS)

Question 3.1:
Do you think a change control (CC) is required for updates (including minor administrative revisions) to an SOP even if the document already has a revision history section?
Answer: This should be defined in your documentation policy/procedure. Some companies choose to use CC for document management; however, this may not be needed nor be appropriate for all organisations, you can use document history no problem and this is more manageable for most organisations.

Question 3.2:
What is a Site Master File (SMF) in the context of GDP? Is it the same as a Quality Manual or does it require to establish a separate SMF if we have a Quality Manual?

Answer: SMF should provide full picture of the company's activities and how it is managed. Usually, a SMF is not seen in a wholesale environment as the Quality Manual will usually suffice. Where wholesale activities are undertaken by a manufacturer then a SMF will be in place. However, the requirements of your competent authority should be followed.

Question 3.3:
Could you provide examples of departments with personnel considered to be involved in wholesale distribution activities?
Answer: This is very dependent on the nature and structure of the company along with how the company is established in relation to roles and responsibilities. Examples may include sales and marketing, operations, finance, reception, warehousing, transportation, quality department, human resources, customer services.

Question 3.4:
Can one Quality Policy be covering multiple companies (e.g. one for several affiliates) or should every company owning a wholesale license have an individual quality policy?
Answer: Usually a company has one Quality Policy covering the Head Office and their affiliates. As long as the policy is relevant to all affiliates, then there is no problem. A Quality Management System should not be confused with Quality Policy.

Question 3.5:
If corporate procedures are available, can they be implemented as such by an affiliate or are specific local procedures required?
Answer: Yes. It depends on the companies' organisation and their document hierarchy regarding which actions need to be taken. As long as all affiliates are part of the same quality system then implementation of Corporate Procedures might be feasible. Again: Depending on the defined document hierarchy and how each of the affiliates is set up to operate. Specific local procedures should be in use where Corporate Procedures are not sufficient to cover differences in affiliate activities. These procedures should constitute the company QMS and follow the same format. Guidance can be sought from the owners of the Corporate Procedures.

Question 3.6:
Is it acceptable if we work with KPI's rather than quality objectives?
Answer: The GDP guidelines referred to quality system objectives and not KPI's; however, you may call them whatever you like as long as the metrics within the guidelines are reviewed and GDP activities are incorporated into your review process.

Question 3.7:
What is the difference between Internal Audit and Self-Inspection?
Answer: These terms tend to be used interchangeably and have different definitions in different companies and different countries. The important part to remember is that you must, as per the GDP guidelines, have implemented a process to routinely review compliance with all aspects of GDP, regulations, guidelines and internal procedures. An Internal Audit could be performed by the RP or another department and the scope could be limited or broad, focusing on a specific area or the whole of the organisation's activities. With regards to GDP, ensuring Self-Inspection is performed is the responsibility of the RP and the schedule needs to cover all the GDP activities undertaken, cross-referencing to the EU GDP Guidelines, reviewing processes, procedures, staff understanding etc.

Question 3.8:
Can QA role be delegated to operation person or person other than QA?
Answer: Due to the varying sizes of wholesalers to whom GDP regulations and guidance are applicable, the GDPs do not define which department personnel must work within. Therefore, it is the responsibility of the individual wholesaler to assess the right person for the right role and ensure their competence and ability to perform that role.

4. Documentation

Question 4.1:
Is the document retention period at least 5 years or can we apply the shelf life plus one year criteria?
Answer: Both are correct. The requirement for GDP is at least 5 years. Manufacturers need to comply with the longest period, so if shelf-life plus 1 year is less than 5 years, then the 5 year requirement applies. Wholesalers must comply with the 5 year retention period, unless holding stock owned by their customer where the customer, for example, requests a longer retention period. Also refer to the requirements of your national legislation and competent authority in the event they require longer than 5 years.

Question 4.2:
Regarding documentation, what requirements are there for hand-written documentation?
Answer: Legible, clear, dated and signed.

Questions 4.3:
What are requirements for GDP documents in comparison with GMP documents?
Answer: There is no difference! Both need to comply with similar standards, there is alignment of documentation chapters in GMP & GDP.

Question 4.4:
Is it okay if we use a seal instead of signatures? The seal will be person specific and controlled.
Answer: No! (There are other opinions on this as well. PIC/S PI 041 states: "The use of personal seals is generally not encouraged; however, where used, seals must be controlled for access. There should be a log which clearly shows traceability between an individual and their personal seal. Use of personal seals must be dated (by the owner), to be deemed acceptable.")

Question 4.5:
Regarding electronic signatures, can AdobeSign or DocuSign be used to sign Technical Agreements, which is a GxP-document?
Answer: Any system or programme used to insert electronic or digital signatures needs to be verified and qualified to GxP requirements.
The UK MHRA has written a guide and a useful blog on this:
https://www.gov.uk/government/publications/electronic-signatures
and
https://www.gov.uk/guidance/approval-of-gxp-documents-when-working-from-home-during-the-coronavirus-covid-19-outbreak

5. Deviations

Question 5.1:
Do we always have to open a deviation in case of damages or temperature excursion during distribution?
Answer: Yes!

Question 5.2:
In big companies, the RP can't approve all deviations himself due to the high numbers of deviations. Can he delegate this approval?
Answer: Yes, but he should ensure those approving deviations are fully trained, and the RP receives reports of these deviations and is aware of critical and major deviations. The RP has final responsibility for GDP deviations.

Question 5.3:
The RP does approve critical/higher risk deviations only from my experience. I think it is efficient to not involve RP in all steps if possible. Otherwise you will create a bottle neck in your organization from my experience.

Answer: We agree, but remember the final responsibility remains with the RP. Minor deviations usually develop to more serious ones in time, therefore the RP should be aware of trends of these deviations and take appropriate actions when required.

Question 5.4:
Is there any requirement for trending of deviations?
Answer: Yes!

Question 5.5:
Is it mandatory that the RP approves a deviation? Or would it be sufficient to align with the RP verbally, mention this alignment in the deviation description and the approval will be conducted by QA personnel?
Answer: It is not a GDP requirement that the RP approves deviations. However, the RP is responsible for ensuring an adequate deviation system is in place. Furthermore, the RP should be made aware of deviations impacting on GDP. Verbal notification is difficult to verify, a better approach may be notifying the RP through email, and then attaching a copy of this email to the deviation. This approach may be challenged from a data integrity perspective, so it should be ensured that email communication is in compliance with your data integrity practices.

6. Complaints

Question 6.1:
Regarding complaints, what is meant with appointing a person to deal with complaints? Where is this stated and what does the responsibility mean?
Answer: This is in the GDP guidelines under Complaints. The person assigned should be trained in handling complaints. In smaller companies this may be the RP, for larger organisations it is easier to assign an individual to manage the process. Responsibility includes for example ensuring product quality complaints are differentiated to those arising from distribution activities, the former should be communicated without delay to the manufacturer/MAH, ensuring procedures clearly defined the flow to route complaints efficiently to the correct person, department or company, ensuring they are handled efficiently and effectively. All complaints should be monitored and trended and reported to key staff and senior management – they provide essential feedback for example on the effectiveness of distribution activities, outsourced activities, changes etc.

Question 6.2:
Is there any standard time defined for closure of complaint? Is there a standard time to reply to the complaint?
Answer: Reasonable timetable should be defined in your procedure and if activities are outsourced, the Quality Agreement (SLA, TQA) must ensure the timelines for communication are clearly described and understood by all parties.

7. Returns

Question 7.1:
When returning the units impacted by a temperature deviation to the stock, should they be labelled and segregated from the rest of the stock even if it is the same batch and SKU number which is difficult to distinguish?
Answer: If a product has been impacted by a temperature deviation and, following an assessment and approval by the RP (or the MAH), is deemed to be suitable to return to stock, then there is no need to segregate or label it as such. However, if this is not the case then it should not be returned to stock.

Question 7.2:
If conditions to move a returned product to saleable stock are not respected, is a deviation required to destroy the product?
Answer: Yes!

Question 7.3:

Is a return always done via a strict reverse logistics? (from A to B, return from B to A → can return to C?)
Answer: It should be, otherwise it will be very difficult to find the history of the product whilst out of your control. All actions should be controlled within SOPs, Contracts and Quality Agreements to ensure product traceability.

8. GDP Certification / Licenses

Question 8.1:
How are license requirements for brokers with respect to virtual companies? If you buy an API in EU, shipped from supplier to manufacturer, is there a license needed and if so what type? The API is never at the broker site and supplier and manufacturer have licenses.
Answer: There is no licensing requirement for brokers, but they have to be registered by the local authorities.

Question 8.2:
Can you clarify difference between Distribution license (WDA) vs GDP certificate vs GDP certification?
Answer: WDA is a license to act as Wholesaler, GDP certificate is issued by the Regulatory Body after their inspection.

Question 8.3:
In what way is GDP applicable to manufacturers, for example a CMO?
Answer: Anytime you store, transport, sell or buy medicines you need to refer to GDP requirements.

Question 8.4:
EudraGMDP: when and how do you use Non-Compliance Reports?
Answer: Non-compliance reports should be checked if a GDP certificate cannot be found for a supplier or customer. Best practice would also be to routinely review non-compliance reports to ensure none are present for your suppliers and customers. Routine checks should be performed to ensure you can continue to trade with your suppliers or customers.

Question 8.5:
If a broker has DP (not FG) manufactured at a contract site and sells outside EU, does that broker need a license and what type? (Product never at the broker site).
Answer: The definition of a broker within EU legislation should be referred to. In general, a broker is relevant to the finished product only and never takes ownership.

9. Qualification of Suppliers

Question 9.1:
Are there some recommendations on what to look at when performing requalification of suppliers? Or is this risk based as well?
Answer: It should be risk based approached.

Question 9.2:
When do you need to perform bona fide checks of suppliers vs. performing audits of your suppliers?
Answer: During an Audit you may want to understand how the supplier is storing and handling product you will procure from them, what are the processes, do they have adequate space and staff numbers for the volume of goods you will procure, how do they handle complaints and feedback. Bona fide checks of suppliers refers to those supplying products to you, this may not be an audit, it is ensuring that they are a legitimate company authorised to sell/supply the product or range of medicinal products.

Question 9.3:
Regarding comply with GDP - if a wholesaler can only provide a WDA but no GDP certificate - what are the due diligence checks for qualification / re-qualification?

Answer: WDA holders in EU and UK are normally inspected by the authorities and if found compliant a GDP certificate is issued. If a company does not have one you need to find out why*, during the audit or bona fide checks. They may have lost their certificate due to non compliance issues. (*Some countries do not issue a GDP certificates after a site-inspection or do not issue a GDP certificate in the first place, the WDA may make a statement to this effect, otherwise you need to request a written statement from the entity you are qualifying, confirming the status and ensure it is backed up by evidence.)

Question 9.4:
Can you sign a Distribution & Quality/ Technical Agreement BEFORE you are issued WDA?
Answer: You can but you can't start operating unless you have WDA.

Question 9.5:
What is behind sales? If we speak about the QMS, which activities are considered as GDP for sales activities?
Answer: Bona fide checks for the suppliers and customers will fall under GDP requirements in relation to the sales department. This activity could also be undertaken by another department, however, sales must ensure they have the most up to date information on the supplier or customer, including checks made on, for example, invoices and shipping notes, entitlement to receive from/sell to, invoice-to and ship-to, prior to procurement or sales activities.

Question 9.6:
Do we need to audit third party security companies?
Answer: Yes.

Question 9.7:
If we have master service agreement and that covers all quality requirements then do we need to make a separate quality agreement?
Answer: No, as long as the MSA covers the required aspects of GDP for your business activities.

Question 9.8:
For quality agreement within a transportation company, if this companies has several offices in the world, which transportation company entities needs to be defined as contract acceptor?
Answer: The contract acceptor is the company accepting to take on work outsourced (or delegated) by another part of the company or a separate company. If the agreement is in place between two or more parties at a higher tier of the company, then the company Quality Manual, QMS and operating procedures should clearly define the tasks, roles and responsibilities for the other offices.

Question 9.9:
Qualification of suppliers is distributor responsibility or the 3PL as well, how exactly responsibilities are established?
Answer: The responsibility for supplier qualification remains with the wholesaler being supplied the product. This activity may be delegated to a 3PL; however, the responsibility remains with the wholesaler. Therefore, the wholesaler should ensure competence of the 3PL, include the activities in an agreement, conduct routine audits of the activity, and ensure that modes of communication are open with the 3PL.

Question 9.10:
Pharma has a lot of M&As. Can you say something about "carry over" of existing Technical Agreements when there is a change in parties?
Answer: The Technical Agreement should be relevant to current practice and business requirements. It should be reviewed when there is a change in parties to ensure it remains valid, current and manageable for all parties concerned – prior to the change in parties.

Question 9.11:
Can you explain the difference between 3PL, 4PL and 5PL providers?
Answer: The definitions for these tend to differ between companies and countries. In general, 3PLs provide storage and transportation services and 4PLs/5PLs provide order processing/receipt and cash

collection services. The important part to remember is that you retain responsibility for all GDP actions conducted under your WDA (authorisation) regardless of whether you outsource these activities or not.

Question 9.12:
Outside of EU it occurs that the Bill To Customer is not the Distributor in territory and doesn't perform any GDP activities and has no QMS; Ship To Customer has GDP qualifications. Is the Bill To Customer an issue from EU GDP point of view?
Answer: The Bill-to customer needs to be qualified so that you have demonstrated the customer has the legal right and appropriate documentation to procure medicinal product. There are nuances to this depending on the reason the bill-to customer is paying for the product, e.g. insurance companies. A clear product and financial flow map will help you decide which entities fall under GDP.

Question 9.13:
Should the qualification of wholesaler include an onsite audit?
Answer: This depends on what role the wholesaler is performing. Suppliers and customers do not require an on-site audit in general. Wholesalers performing 3PL activities on behalf of partner should be audited. A risk-based approach could be taken to perform a remote audit either online (think about the current challenges in practice due to the coronavirus pandemic) or a desk-top audit (e.g. questionnaire type audit). Remember to justify and retain your decision within your QMS.

10. Batch Control

Question 10.1:
Is there any paragraph or law that forced manufacturers to provide wholesalers/clients with COA and batch release? If not, how can medicine agencies expect us wholesalers to obtain it when no law forces manufacturers to provide us with the document?
Answer: There is no law (GMP/GDP regulation) requiring manufacturers to provide COA to their customers, however the purchaser is obliged by law to buy medicines from authorized suppliers, in compliance with the GMP/GDP regulations ensuring the products meets the market registered details. This can only be achieved by a document issued by the manufacturer stating that their product was manufactured in line with the EU requirements and GMP, COA is one option to do this.

Question 10.2:
Administrative Batch Control for GDP: Can you address how different EU CAs are implementing this?
Answers: All CA's require you be able to demonstrate that you have performed proper due diligence, regarding the supplier of product, checked the transportation conditions and how product has been handled from supplier to your facility, including its temperature conditions. How to achieve this is up to the companies and the RP to define and justify, a process as described during this course as best practice, alternatives will be possible as long as you can demonstrate you have achieved all the above.

11. Storage and Warehousing

Question 11.1:
If the entire facility is accessed control does it require to build separate access control case or facility for narcotic drugs?
Answer: Access control for Narcotics storage may be required by individual member states, e.g. in the UK the Home Office has very detailed requirement for these storage facilities. Check with your local authorities to understand the exact requirements in your country.

Question 11.2:
What is the time limit for products being stored before facility is classified as storage? 24h? 36h?
Answer: The final version EU GDP does not define a specific timeline. Nevertheless, some local adaptions, e.g. Ireland, specify time limits. You need to demonstrate product integrity has been maintained at all times during storage, transportation, at hubs, cross-docking stations, in transit etc.

Question 11.3:
Is emergency exit is the requirement of GDP? how many emergency exit require for warehouse or how measure it?
Answer: No, but it is a health & safety requirement, the number depends on the site of facility and risks involved.

Question 11.4:
Is it mandatory to have change room for warehouse?
Answer: You should avoid staff entering the warehouse with outdoor clothing and shoes etc. to avoid contamination, e.g. mud in winter, wet clothes during rainy day etc. Therefore a changing room is needed to facilitate this.

Question 11.5:
Do expired, recalled or rejected products require to store lock and key controlled area?
Answer: GDP states they should be securely separated. How to achieve this up to you, but should be able to demonstrate the security of these materials.

Question 11.6:
I am not clear do you mean veterinary medicinal products and human products can not be stored in the same warehouse?
Answer: Medicinal products for human use should be stored separately from medicinal products for veterinary use. This could be by segregation (physical or electronic) within the same warehouse, with assured practices to prevent product mix-up. In any case it must be ensured that quality of the product is not compromised. For example, in case veterinary product has a strong odor it might be attractive for pests and have a negative influence on other products stored aside. This must be considered.

Question 11.7:
As you said receive the products directly into the respective area according to storage condition, does it require to create receiving area in every category of storage area?
Answer: No, however all product should be handled efficiently according to its labelled requirements. E.g., frozen and refrigerated goods will need to be handled in the shortest possible time-period to ensure product is not inadvertently exposed to temperature deviations, narcotics (controlled drugs) need be handled efficiently – the receiving area needs to be of sufficient size to properly and efficiently handle the volume of goods received.

Question 11.8:
One warehouse has only one area for product receiving and dispatch. The warehouse has to ensure segregation by time. E.g., receiving done from 4-8 pm and dispatch done from 8-12 pm. is it ok from GDP point of view?
Answer: This is dependent on the country in which the wholesaler is based, i.e., some competent authorities accept this and some do not. If acceptable in principle, the wholesaler should ensure that the area is completely clear between the two activities; the methods for managing the area should be defined in a procedure, and all personnel well-trained.

Question 11.9:
If a temperature excursion occurs during storage and a temperature assessment is performed, who must approve the assessment? Is it mandatory that the local RP approve the assessment and provide the release letter? Or can it be delegated to QA personnel?
Answer: The RP can delegate duties but not responsibilities. The RP remains responsible for final assessment of the product.

12. Temperature Mapping

Question 12.1:
How to decide total number of temperature probes required for a specific area qualification or temperature mapping study?
Answer: This is not an easy task, there are some calculations you can do, but generally you must ensure all key areas of risk are covered, e.g., coolest and hot part of the warehouse, near doors, windows,

heater, air ducts, sky lights, at high, middle and low levels. The idea is to ensure you have a good coverage of the temperature profile of the area you are mapping. Once mapping is complete based on the data collated you can decide the most appropriate locations for ongoing monitoring, the number of thee will depend on the result of the mapping.

Question 12.2:
Does the regulation require to execute temperature mapping during summer and also during winter times?
Answer: Yes, you should be ale to demonstrate you can maintain the warehouse temperature all the year round, hence the need for mapping in summer and winter.

Question 12.3:
During mapping how many temperature probes are required as per standard?
Answer: There is no standard available. We would recommend to approach a company that is expert in temperature monitoring/mapping to develop a plan together with you.

Question 12.4:
How to define and identify the hot spot or cold spot to monitor continuously?
Answer: This is the result of the temperature mapping that you have conducted. Typically, next to doors, next to air conditioning units or on the top shelf hot or cold spots can be found.

Question 12.5:
If one warehouse has temperature rang 2-8C and if during mapping it is found at three (among 20 points mapped) points maximum temperature resides at higher side, e.g. 7C, 6.7C, 7.5C. Do I need to consider all these 3 points as hot spot & to monitor continuously?
Answer: Could be appropriate.

13. Validation

Question 13.1:
I have noticed that in practice the applying of validation requirements vary depending of the sensitivity of the products. What are your comments to that?
Answer: Validation should be risk based and relevant to the subject, ensuring you can demonstrate the system validated can operate consistently delivering the expected output.

Question 13.2:
For Computerized system, all aspects of Data Integrity will apply?
Answer: Yes!

6.3 Questions and Answers on Data Integrity

1. Is it necessary to carry out a Data Integrity Assessment? Which areas must be covered by such an assessment? Does the management need to be involved?

Eberhard Kwiatkowski, PharmAdvantage
The integrity of data must always be verified!

An assessment with pre-defined questions can only be performed for operating systems that have not yet been DI-checked. The assessment should help to recognize the gaps and to take suitable measures. A prioritization of the systems with respect to the period of implementation of the activities has also to be done. At this point, the management comes into play and must provide the necessary resources to be able to carry out the activities.

2. Must data flow diagrams be available?

Karl-Heinz Menges
Annex 11 to the GMP Guidelines requires that a current system description must be available for critical systems, which also reflects the data flow.
The PIC/S document PI 041 mentions data flow diagrams in connection with risk assessment: 5.5.3 Risk assessments should focus on a business process (e.g. production, QC), evaluate data flows and the methods of generating and processing data, and not just consider IT system functionality or complexity.
9.1.5 When determining data vulnerability and risk, it is important that the computerised system is considered in the context of its use within the business process. ... The creation and assessment of a data flow map may be useful in understanding the risks and vulnerabilities of computerised systems, particularly interfaced systems.
If one comes to the conclusion that a data flow diagram is not necessary for a concrete system, the rationale for it should be documented.

3. Do specific training programmes in manufacturing and quality control need to be in place to sensitise employees to the topic of data integrity?

Dr Wolfgang Schumacher
All guidelines on data integrity published in recent years require specific training for personnel; in addition to general information for employees, all persons involved in GMP should receive special intensive training. The topics include both the documents issued by the management on data governance and the detailed regulations (e.g. on the Audit Trail Review) with regard to production and QA/QC.

4. Is it necessary to define which data must be retained in which form and for how long? Does this definition have to be specific to the method or process or is a comprehensive definition expected?

Karl-Heinz Menges
It is essential to determine which data must be retained and for how long in order to comply with legal requirements. The German Medicines Act (AMWHV) specifies in detail how long documents must be retained. If necessary, requirements of other legal areas that go beyond this must also be observed. It is up to the regulated user to decide whether he/she wishes to carry out these specifications across all areas or product-specifically.

5. Are there specifications regarding who and to what extent a data review must be carried out and how the results should be documented?

Eberhard Kwiatkowski, PharmAdvantage
There are no detailed specifications for the data review. It depends on the criticality of the data generated or processed and must be defined by the pharmaceutical manufacturer. This also includes the type of documentation. It makes sense to create checklists. These can be made in electronic form

as well as on paper. What is important is that an evaluation is carried out and documented. The Qualified Person is responsible for this.

6. If GMP-relevant data is created and "delivered" by third parties, how does it have to be ensured and verified that the contract manufacturers / contract laboratories / service providers also meet the data integrity requirements (ALCOA+)?

Dr Wolfgang Schumacher
When data is provided by contract manufacturers, contract laboratories or other service providers, the final responsibility always remains with the pharmaceutical manufacturer. The data integrity requirements must be clearly specified in the contract or SLA (Service Level Agreement) for the delimitation of pharmaceutical responsibility. This also includes an information obligation on the part of the contractor, who must inform the customer immediately of the discovery of a data integrity issue (e.g. within one day).

7. Must there be regulations for remote access by service providers to GxP-critical systems? What data integrity requirements must be included?

Dr Arno Terhechte, Bezirksregierung Münster (District Government of Münster)
Remote access enables service providers to access computerised systems via a network connection aiming at troubleshooting or changing the configuration. Where a GxP critical computerised system is accessed remotely, the activities of the service provider or service company may alter the system so that it no longer remains validated. Therefore, remote access and actions performed during this session should be controlled and documented. This means that the access should be actively enabled by the RU (regulated user) and that it should take place via a secure network connection. Besides, it should be noted which activities were carried out within the scope of the access. If necessary, a change control process should be initiated. The aim is to maintain and control the validated state of the system.

8. What agreements need to be included in contracts with cloud service providers in order to ensure data integrity?

Dr Arno Terhechte, Bezirksregierung Münster (District Government of Münster)

The introduction of cloud services into the GMP environment increases. The cost factor dominates the discussion; however, specific risks need to be taken into consideration. Especially the issue of data integrity in cloud applications is not to be underestimated. What agreements need to be included in contracts with cloud service providers in order to ensure data integrity?

The necessity for contractual agreements is laid down in chapter 7 "Outsourced Activities" of the EU GMP Guidelines as well as in Annex 11 "Computerized Systems" of the guidance. The following are requirements for contractual agreements between a Regulated User (RU) and a Cloud Service Provider (CSP) which are meant to ensure the integrity of data (in motion and at rest). These requirements cannot explicitly be found in the EU GMP Guidelines, they should however be considered as useful:

- Data transfer should only occur in encrypted form and in a way which ensures that the data being transferred are complete and unchanged.
- CSP handling sensitive data or data with high availability requirements must have a certified ISMS (Information Security Management System) in place (e.g. as per DIN 27001).
- CSP handling sensitive data or data with high criticality must submit to penetration testing in the course of their qualification.
- Sensitive or critical data may only be stored in encrypted (or pseudonymized) form.
- A deployment model should be chosen based on criticality. Private or community cloud models should be chosen rather than a public cloud for sensitive data.
- Sharing data with a third party (e.g. subcontractors), e.g. providing infrastructure (storage space for backups, redundant computing power, etc) should be prohibited or dependent on the RU's approval.

- The deletion of data must be fully guaranteed.
- It must be possible to export data in a way that allows RUs to switch CSPs or get the data back on premise.
- Only a limited, specifically selected and qualified group of people from the CSP should be able to access the data.
- If data has been encrypted, the key management should lie with the RU.
- The CSP informs the RU about changes which might impact the application or database. A notification of change with release note is expected, ideally issued before the actual implementation of the change so that the RU may check the effects of those changes, if necessary.

9. Which regulations are necessary as to how the data is completely returned to the client in the event of the closure (insolvency) of a cloud service provider (CSP)?

Dr Arno Terhechte, Bezirksregierung Münster (District Government of Münster)
Both the German Act (AMWHV) and the EU GMP Guidelines see the responsibility in the RU. The AMWHV focuses on the retention of documentation, i.e. the availability of GxP-critical data. According to § 20 AMWHV, in the event of closure of the manufacturing or testing facility in which the documentation is stored in accordance with clause 1, the pharmaceutical company must take provisions to ensure that the documentation is retained for the entire storage period.
The EU GMP Guide focuses on the business process and thus on the GxP-critical application and the data. According to Annex 11 to the EU GMP Guidelines, Chapter 16 Business Continuity, provisions should be made to ensure continuity of support for those processes in the event of a system breakdown (e.g. a manual or alternative system), when computerised systems support critical processes. The time required to bring the alternative arrangements into use should be based on risk and appropriate for a particular system and the business process it supports. These arrangements should be adequately documented and tested.
This task / obligation could be included in the service contract with the CSP by obliging the CSP to ensure the availability of data and, where appropriate, application through an additional subcontractor.
However, the RU should evaluate in a risk assessment whether it would not make sense to maintain a backup site on premise.

10. Do existing QA systems need to be checked for adequacy of the rules to ensure data integrity in electronic and paper-based systems? What points need to be particularly taken into account here?

Dr Thierry Dietrich
Not only the WHO, but also the EMA, the FDA, the MHRA and the PIC/S expect regular or even continuous monitoring of the effectiveness of established procedures aimed at ensuring data integrity (self-inspections, internal audits, etc.). Preventive measures must be taken if weak points are identified in the quality management system that could lead to data integrity incidents (preventive actions).
For concrete data integrity incidents, established procedures must be followed in order to investigate them appropriately and to ensure that they cannot occur again in the future (deviations/NC/corrective actions).
These aren't surprising requirements but absolutely consequential ones. The data management system to ensure (among other things) data integrity should be an integral part of the quality management system. For the latter, the requirements above apply and thus also apply implicitly to its components. For both aspects, established quality management systems should therefore already include suitable procedures.
The data integrity analyses or related risk analyses which are also expected by the WHO, the EMA, the FDA, the MHRA and the PIC/S reveal which items should be given special attention. If a new data management system is introduced, tools such as gap analysis could help to identify any gaps or weaknesses in the quality management system with regard to data management.

11. Do all worksheets, production records, test records etc. have to be uniquely identified? How must the issue and the return of worksheets be checked?

Karl-Heinz Menges
Chapter 4 of the EU GMP Guidelines requires the following: "*documents should ... be uniquely identifiable.*"
This requirement is interpreted by some authors to mean that each piece of paper in a pharmaceutical company must be given an individual number but it is ignored that requirements for instruction documents are laid down in EU GMP Chapter 4 section *„4.3 Documents containing instructions should be approved, signed and dated by appropriate and authorised persons. Documents should have unambiguous contents and be uniquely identifiable. The effective date should be defined."*

12. How must it be ensured for electronic systems that employees can only carry out actions that correspond to their specific tasks (need to know, need to have)?

Frank Behnisch, CSL Behring
Annex 11, § 12 describes this very clearly: " Physical and/or logical controls should be in place to restrict access to computerised system to authorised persons. Suitable methods of preventing unauthorised entry to the system may include the use of keys, pass cards, personal codes with passwords, biometrics, restricted access to computer equipment and data storage areas. The extent of security controls depends on the criticality of the computerised system. Management systems for data and for documents should be designed to record the identity of operators entering, changing, confirming or deleting data including date and time." There is little to add. In practice, this means a concept of role and rights that is oriented to the requirements of the supported process. For example, it can be guaranteed that the operator may only carry out the steps described in the SOP he or she has also been trained for or which correspond to his/her level of training and his/her function in the company.

13. How do risks to modify or delete GxP-critical electronic data (unintentionally or intentionally) need to be addressed in the risk analysis of computerised systems?

Thierry Dietrich
Data integrity requirements must be considered in risk analyses according to the WHO, the EMA, the FDA, the MHRA and the PIC/S. It is up to the responsible party whether this is done in a so-called "risk analysis of computerised systems", in a specific data integrity risk analysis or other risk analyses.
There are also no specific requirements as to how such risks should be addressed. This is also not possible because the individual uses of computerised systems will differ greatly from one another even within a single company. In a computerised system, which is mainly used to produce electronic GxP documentation, it could be possible and useful to completely prevent the modification or deletion of entries made, if these are recorded electronically (e.g. if a temperature sensor passes a measured value directly on to the recording system). In the case of manual recording, this may be undesirable.
A risk analysis should identify and analyse risks specific to the process and computer system for critical GxP data and, if necessary, define appropriate specific countermeasures.

14. Do data need to be stored in the native format or converted to an application-independent format?

Wolfgang Schumacher
Dynamic data must be stored in the native data format to enable reprocessing. Static data needn't to be stored; the printout is sufficient.

15. Does the deletion of data have to be regulated in a SOP?

Klaus Feuerhelm Regierungspräsidium Tübingen

Deleting GMP-relevant data is considered critical. The deletion of GMP-relevant data in a computerised system must be recorded by an audit trail. Annex 11 of the EU-GMP Guidelines states:

"12.4 Management systems for data and for documents should be designed to record the identity of operators entering, changing, confirming or deleting data including date and time."

Basically, it must be possible to recognize who is deleting data within such systems. Deleting data endangers data integrity and is a critical step. Work steps must be described in standard operating procedures (SOPs):

Chapter 4 of the EU-GMP Guidelines - Required GMP Documentation:
"Procedures: (Otherwise known as Standard Operating Procedures, or SOPs), give directions for performing certain operations."

Deleting data that is no longer required is allowed. Deletion is the last step in the data life cycle. Safe procedures must be established for the deletion of GMP data.

Data should normally only be deleted after the end of their retention period. There are very few exceptions as to when data may be deleted before the end of its retention period. This includes, for example, data that has been migrated to another system. The deletion of data must be described in detail in a relevant SOP.

16. Is it necessary to harden computerised systems to prevent accidental changes to data and metadata?

Thierry Dietrich
Although this would be an ideal objective, it will certainly not be possible in all cases.
This should be achieved where the intended use and the technology employed in a computerised system allow for the total prohibition of changes to critical data and metadata.
However, it is also possible that:
- the intended use of the system does not permit this,
- the system cannot detect whether a change is intended or unintended; or
- this is technically not feasible.
In these cases, a risk analysis should be carried out to examine whether and which alternative control measures should be taken to bring the risk to an acceptable level.

17. How to ensure data integrity when transferring data from one computer system to another (data in motion)?

Wolfgang Schumacher
The best way for data transfer between systems is a direct interface without intermediate storage. If this is not possible, or if the data is transferred via the Internet or an unsecured data connection, for example, the data should be encrypted.

18. Does a training programme on data integrity need to be established in a company? What must be included in this training programme?

Dr Wolfgang Schumacher
The topic of data integrity must be integrated into the routine training programme of pharmaceutical companies. All employees working in GMP must be trained in the details of data integrity. This includes in particular those processes in which employees have forgotten entries in protocols, for example, which must be later performed out in compliance with GMP. A training programme should also draw attention to the consequences of knowingly making false entries (falsifications) for the employee (warning, dismissal).

19. What must be addressed regarding data integrity in the auditing of contract manufacturers? Is a standard operating procedure necessary for this?

Wolfgang Schumacher
An appropriate paragraph shall be included in the delimitation agreement to ensure data integrity. In this paragraph, the contractor shall be obliged to inform the client immediately in the event of DI issues. Furthermore, the audit should verify whether third parties (e.g. cloud service providers) have been commissioned to store data. If external manufacturers or testing laboratories are used for the manufacture or testing of the products, the secure transmission of the batch records, for example, is very important: the e-mail system must NOT be used for this purpose. The topic of data integrity

should be included in the SOP "Auditing of contract manufacturers", together with corresponding audit questions.

20. Must there be a concept for evaluating the criticality of data? And what rules for entering critical data into computerised systems must be available?

Klaus Feuerhelm, Regierungspräsidium Tübingen

The evaluation of data with regard to criticality is essential and - to some extent - no trivial activity. Data must be evaluated in particular with regard to patient safety and/or product quality.

The term "critical data" appears at only one place in the EU GMP Guidelines:

"4.27 - A system should be in place to indicate special observations and any changes to critical data."

The EU GMP Annex 11 also mentions critical data at only one place.

"6. Accuracy Checks - For critical data entered manually, there should be an additional check on the accuracy of the data."

This provides a legal basis for reviewing the entry of critical data. A second person must therefore verify it. An alternative would be a validated computerised system.

Example:
The temperature is measured in a stirring tank. This measurement is part of the batch report and is relevant for release. The temperature is read manually and documented manually. In this case, a second person is required to check the correctness of the data (double-checking principle).

or

The temperature is recorded electronically via a computerised system and saved electronically. In this case, the computerised system would have to be validated.

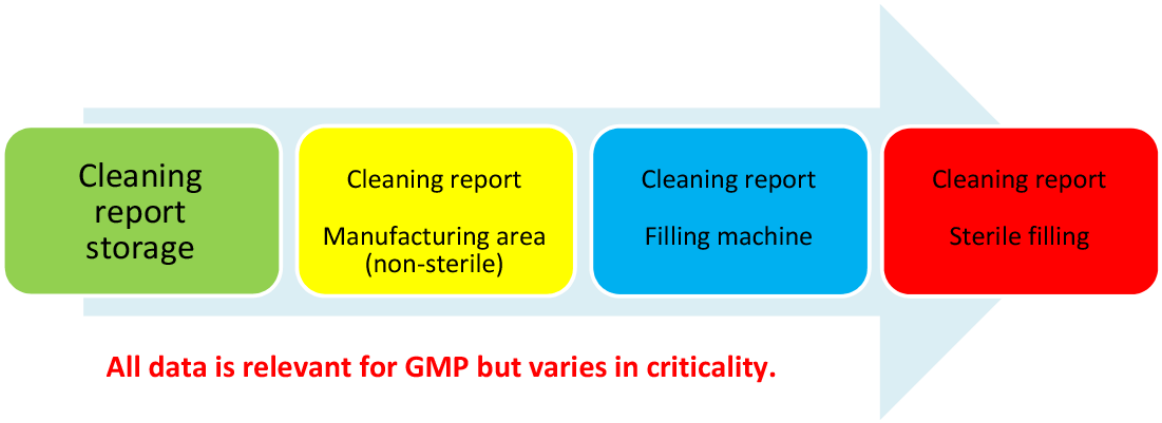
Back to the evaluation of data criticality: neither section 4.27 nor Annex 11 (section 6) provides much information about which data is critical and which is not. There is no legal definition of critical data in the GMP environment. If one looks at the various guidelines and standards in the GMP area, a definition for critical data can be found in VDI/VDE 3516 Part 5 on "Validation in the GxP environment - Types of raw data":

"Critical data:
Data that has a potential impact on patient safety, product quality and data integrity".

It is the decision of the company (medicinal products manufacturer) to define the data to be included.

The crucial question is certainly: Is there any GMP-relevant data which is not critical?

This cannot be answered unequivocally from the contents of the current legal bases. However, the answer "No" is the productive one. Yet, there are differences in the criticality of data. Figure 1 shows a corresponding example. A three-level classification makes sense:



Criticality is high, medium or low.

PI 041 GOOD PRACTICES FOR DATA MANAGEMENT AND INTEGRITY IN REGULATED GMP/GDP ENVIRONMENTS provides information on critical data, which also proves their significance.

Example:
"5.4 Data criticality - For example: for an oral tablet, API assay data is of generally greater impact to product quality and safety than tablet friability data".

The document stresses the importance of data in terms of its influence on decisions such as the batch release.

"5.4 Data criticality
5.4.1 The decision that data influences may differ in importance and the impact of the data to a decision may also vary. Points to consider regarding data criticality include:
Which decision does the data influence?
For example: when making a batch release decision, data which determines compliance with critical quality attributes is normally of greater importance than warehouse cleaning records"

21. Are regulations necessary for the handling and management of data generated by small systems (e.g. pH meters, filter integrity testers, etc.)?

Klaus Feuerhelm, Regierungspräsidium Tübingen

As a rule, GMP-relevant data must be documented. It doesn't matter if this data is generated by large or small systems. Basically, the handling of this data must be regulated.

GMP-relevant data from small computerised systems may have to be read directly from the device and written down by hand. If the system has a printer interface, this interface should also be used. This is an essential step to ensure data integrity.

This also means that when purchasing such small systems, one should already make sure that they have a printer interface. The printer ensures an independent and correct recording of the data when the system is qualified. Raw data is demonstrably available:

MHRA 'GxP' Data Integrity Guidance und Definitions from March 2018:
6.2 "In the case of basic electronic equipment that does not store electronic data,or provides only a printed data output (e.g. balances or pH meters), then the printout constitutes the raw data."

Especially with small systems, it is possible to manipulate data. Restrictive requirements for the handling and documentation of such data are mandatory.

The MHRA 'GXP' Data Integrity Guidance and Definitions document from March 2018, for example, refers to this risk:
4.3 "Within these systems, it may be possible to manipulate data or repeat testing to achieve the desired outcome with limited opportunity for detection (e.g. stand-alone systems with a user-configurable output such as ECG machines, FTIR, UV spectrophotometers)."

22. Do administrator rights have to be separated from the business process user, including master data management (workflow, critical parameters, etc.)?

Dr Wolfgang Schumacher
Administrators usually have extensive rights for the systems they manage; they can add, change or delete GMP-relevant data. It must be ensured that the administrator doesn't influence such data. This is best done by clearly assigning the GMP activities in the user or administrator profiles. In the production area, critical machine parameters should be set to the specified target values (according to the specifications) by a function independent from the operator (e.g. engineering). This ensures that the operator can only make limited changes to the settings within the approved "Design Space".

23. Does the system need to protect the data by preventing deletions by the operator?

Frank Behnisch, CSL Behring
Deletions by the operator are not categorically excluded. This must be defined in accordance with the process requirements and evaluated on the basis of the risk. At least, however, an audit trail must be established that records the deletions including the audit trail data (who, when, deleted or changed from what to what and why). Data can be deleted at the end of the retention period.
Depending on the process security requirements, it may be advisable to protect the deletion of data with rights.

24. Do all users have to log in using unique user IDs?

Frank Behnisch, CSL Behring
Yes. This is laid down in Annex 11, §12 as well as in the US-American 21CFR Part 11. A group password is not acceptable.

25. How do I practically proceed if I want to recognize the state of DI in the company? How do I document it?

Dr Wolfgang Schumacher
The status of implementation of a data integrity concept in the company can best be determined by means of a gap analysis. The policies issued by the company management (DI Policy, DI SOP) and the evaluation of the implemented computerised systems in production and quality control are checked. These include in particular the so-called "Segregation of Duties" and the regular review of the audit trails in the quality-relevant systems. The gap analysis should be regularly reviewed and updated. It is used during an official inspection to prove the current DI status.

26. What influence does IT technology have on data integrity (e.g. Active Directory, DNS, Citrix, Windows systems, authorization concepts ....)?

Thierry Dietrich
This is a very complex and broad question.
Basically, it can be stated that IT:
- brings with it new data integrity risks that did not exist in the obsolete paper process.
- enables technical risk control measures that help reduce or better control data integrity risks that were previously unavailable in paper-based processes.
Thus, the IT used can have both positive and negative effects on data integrity. In addition to the inherent risks and opportunities compared to paper-based systems, the implemented IT design can also have a positive or negative impact on data integrity. Different software and hardware architectures can have distinct risks with regard to data integrity.
Examples of technologies have already been listed in the question. MS Active Directory (properly implemented) can help to securely manage identities, secure access to GxP applications, secure

access to GxP data, and identify users more securely in the event of data changes (audit trail) or electronic signatures. However, there are other products on the market for this purpose. Such technologies are highly relevant to data integrity.
Citrix architectures (correctly implemented) can also improve the control of data integrity risks, as access to the application and to the data can be technically more restrictive. The technical implementation and the intended use of the application are very important here.
Authorisation concepts become more and more important with the increasing complexity of a computerised system (number of users, number of roles, number of functionalities, etc.). The existence or non-existence of a professional authorisation management system within a computerised system and its functional scope can therefore have a considerable influence on data integrity.

27. What are the implications of updates, patches, hotfixes, etc. for data integrity in the regulated area? What do I have to do when installing?

Frank Behnisch, CSL Behring
Patches, hotfixes and updates are also changes. As such, they must also be handled according to the company's change control procedures. At least an evaluation of the possible effects on the validated system is required. Based on this, appropriate measures up to change validation with regression testing may have to be defined. In the best case scenario, the risk assessment ensures that there is a high probability that no undesirable effects on the application can be expected (e.g. in the case of simple infrastructure measures such as the update of switches) and that further measures are not required.

28. How can I handle analysis devices that are connected to a LIMS via a middleware? The manufacturer does not allow access to the original data in the automated analyser though.

Eberhard Kwiatkowski, PharmAdvantage

This question considers raw data to be the same as generating the first data. This is not recommended. In the GMP environment, the raw data should be defined by the pharmaceutical manufacturer. The type of data generated is important for defining it. Is static data or dynamic data available? If the data is static, the raw data can consist of cumulative primary data (first generated data). In the case of dynamic data, raw data can be the original data.

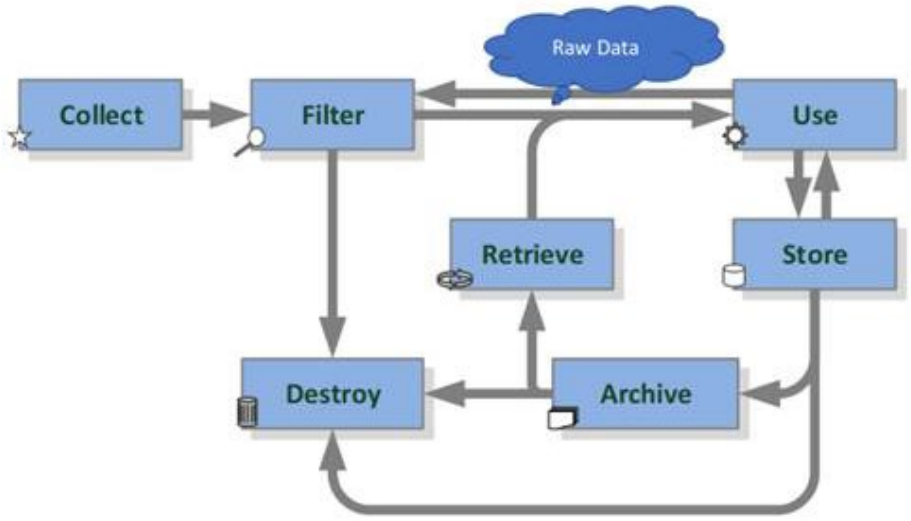
The following definitions are necessary for answering this question:

Original Data:
This represents the first recording of the data which is kept in the first storage location (e.g. analogue data).

Primary Data:
This is processed data that leads to the result on the respective device. If this data is collected on the device of origin, it can also be considered as original data (e.g. digital data calculated from an analogue signal).

Raw Data:
This is the specified data (from the totality of all available data) necessary for the reconstruction and evaluation of the derived outcome data relevant to patient safety, study results and/or product quality.

The data life cycle (see figure below) shows that raw data can be defined by the evaluation.



Once the output data which is definitely required has been defined, the second step is to determine which input data (e.g. individual values) is necessary on the basis of the available data processing methods and which processing methods are needed for this.

In addition to the definition of the data types, it is also important to determine whether all individual values are required as raw data in order to be able to reproduce the result. If traceability is no longer possible because the generated data is not available in the LIMS, this process is not "compliant". In this case at best, validation can provide help: it must be proven that all relevant (to be defined) data is transferred to the LIMS in order to check the plausibility (traceability) of the result.

29. Do the analytical data count as critical data in the course of validation of analytical procedures?

Thierry Dietrich
First of all, data can only be as critical as the process itself that generates it. If a process is not critical in itself, the data is not.
In a critical analytical procedure where its result has a direct influence on the release of a batch for example, the corresponding result data is - of course - also critical.
The data generated during the validation of a procedure is essential for the documented evidence of the suitability of the analytical procedure. If this data is missing or if it is not of integrity, the suitability of a critical analytical procedure cannot be systematically proven. Thus, even all (critical) individual results from this procedure would no longer be trustworthy, i.e. no longer of integrity. In this respect, the validation data of a critical analytical procedure can also be considered critical.

30. Is it necessary to retain and archive all electronic data during a sterile process or is the batch record sufficient?

Thierry Dietrich
Archiving is merely a long-term storage method (among others) with slower access times. This applies to both paper and electronic records (which in turn contain data). There is no archiving obligation. However, there are requirements for retention periods with different times depending on the type of recording as well as requirements for access times (e.g. as part of an inspection).
A batch record can be paper-based, electronic or hybrid (paper-based and electronic). The above question seems to relate to cases where the data required to generate the batch record originates from an electronic "source system" (e.g. a LIMS, MES or ERP system) and it seems to be the question whether the data concerned must be stored electronically in addition to the batch record in the source system or in some other way.
The FDA writes in its guideline for data integrity published in the middle of December 2018 that a transfer of "cGMP records" which were available in their original form as "dynamic data", into a paper

or "static" copy did not satisfy the requirement of §211.180(d). Such copies did not represent original records or true copies in the sense of the law and could, for example, not be re-processed and possibly be incomplete.
The MHRA also demands in its final guideline on data integrity dated March 2018 that data should be kept in a dynamic form if this is necessary to maintain their integrity or for later verification. The PIC/S demands this analogously in the 3rd draft of the guideline PI041-1 of November 2018 and the WHO in its draft guideline of September 2015, if the dynamic nature of electronic data is important for the content and significance of a recording.

Audit Trail

1. Changes and deletions of GxP-critical data must be tracked via an audit trail. What measures must be taken if the systems do not have this functionality?

Karl-Heinz Menges
If a system does not have an audit trail functionality, it should first be checked whether data can either be blocked or restricted to a specific group of users by means of appropriate rights, changes, and deletions. There must be a SOP which specifies how changes and deletions must be documented by these users and who must be informed about the activity and how. These should be at least those persons who make decisions about the quality of a product or material based on the changed data.

2. Is the Audit Trail review required by the authorities before each batch release, or is it only recommended?

Klaus Feuerhelm, Regierungspräsidium Tübingen

The requirements for the Audit Trail and its review are formulated in Annex 11 of the EU GMP Guidelines: 9 Audit Trails: "*Consideration should be given, based on a risk assessment, to building into the system the creation of a record of all GMP-relevant changes and deletions (a system generated "audit trail").* For change or deletion of GMP-relevant data *the reason should be documented. Audit trails need to be available and convertible to a generally intelligible form and regularly reviewed*". The reason for the change or deletion of GMP-relevant data should be documented. Audit Trails must be available, convertible into a generally readable form and regularly reviewed.

If one first looks at the information provided by the legal basis of EU-GMP Annex 11 Section 9 Audit Trails, there are no concrete instructions as to when an Audit Trail is to be reviewed. Here, you can only find the specification concerning the regular examination:

"*Audit Trails must be available, convertible into a generally readable form and checked regularly*".

The EU GMP Annex 11 Section 8 "Printouts" is much more concrete:
"8.2 – *For records supporting batch release it should be possible to generate printouts indicating if any of the data has been changed since the original entry*."

Conclusion:

This clearly addresses the documentation related to lot release and involves modified data. This can only mean that an Audit Trail check of the data to be seen in connection with the batch release must also be checked before the release.

Although the PIC/S document PI 041 GOOD PRACTICES FOR DATA MANAGEMENT AND INTEGRITY IN REGULATED GMP/GDP ENVIRONMENTS doesn't constitute a legal basis, it can be assumed that inspectors worldwide will follow the provisions and requirements of this guidance. Here, it is again confirmed that all Audit Trails to be seen in connection with batch release must also be reviewed before release:

"9.4 Audit trails for computerised systems: Critical audit trails related to each operation should be independently reviewed with all other records related to the operation and prior to the review of the completion of the operation, e.g. prior to batch release, so as to ensure that critical data and changes to it are acceptable."

3. What can be done if an audit trail upgrade is not possible for a hybrid system?

Karl-Heinz Menges
Procedural measures must be taken to ensure that changes to GMP-relevant data are documented in accordance with the rules of Good Documentation Practice. The company should have a measures action plan which specifies the sequence in which systems without an audit trail are to be replaced. This should be based on a documented risk analysis.

4. May the laboratory manager have administrator rights, e.g. to perform the audit trail review?

Eberhard Kwiatkowski, PharmAdvantage
Here, reference should be made to the conflict of interest. Anyone, including the laboratory manager, who generates, processes and/or releases data may not be an administrator!
The report for the audit trail can be generated by the administrator. However, this report is not operationally active for this system.

5. How to handle old devices if there is no audit trail available or a "user login" is not possible?

Klaus Feuerhelm, Regierungspräsidium Tübingen
First of all, it is clear from the contents of the Annex 11 to the EU GMP Guide that an audit trail should be available in connection with GMP-relevant data and their modification in a computerised system. If this functionality had not been available at the time the system was acquired, it should first be checked whether an update with the audit trail functionality is now available for the system. If this is not the case, a corresponding alternative should be provided. EU GMP Annex 11 does not describe what this alternative should look like.
One possibility would be to use handwritten audit trail logbooks. This alternative is also suggested by the *PIC/S in the document PI 041 GOOD PRACTICES FOR DATA MANAGEMENT AND INTEGRITY IN REGULATED GMP/GDP ENVIRONMENTS:*
9.4 Audit trails for computerised systems:
If no electronic audit trail system exists a paper based record to demonstrate changes to data may be acceptable until a fully audit trailed (integrated system or independent audit software using a validated interface) system becomes available. These hybrid systems are permitted, where they achieve equivalence to integrated audit trail, such as described in Annex 11 of the PIC/S GMP Guide.

6. Devices/equipment often have standard audit trail functions. A lot of data is recorded (on/off) and only a small fraction is critical and relevant for reviews. What is the best way to proceed with?

Frank Behnisch, CSL Behring
The perception has changed especially with regard to the audit trail. Before the revision of the Annex 11, the general point of view was the preservation of evidence in order to have further data available in case of a deviation. Also statements of the American authority (FDA) nourished this point of view: in their Dockets it is stated: "Audit Trail... we may use it for a useful purpose e.g prosecution". As a result, the focus in the software was not on later evaluability, but on recording. Therefore, the audit trail data was simply stored sequentially in tables. So far, there are only a few systems that fully support the new requirements. Now, with the additional demand, also including the reason for the change, there are further demands on the systems and also further sorting criteria. In addition, it was clarified that the audit trail can be limited according to a risk-based procedure. Here, the opportunity lies in the limitation to the essential data. Both Annex 11 §9 as well as Chapter 4 of the EU GMP Guidelines describe what these are. Further information can be found in the "Aide Memoire" (Aide-mémoire 07121202) published in the ZLG, where the following quotation can be found: "1 - Based on a risk assessment, consideration should be given to integrating the recording of all GMP-relevant

changes and deletions into the system (a system-generated "audit trail"). 2 - When changing or deleting GMP relevant data, the reason should be documented. 3 - Audit trails must be available, be legible and regularly reviewed.". Therefore, it makes sense to first derive the definition of the relevant data for the audit trail from the definition of the raw data, in order to then determine for which data a review must be performed and which assessment criteria must be applied. This is in line with the requirements laid down in Chapter 4, where it is stated that at least the data on which a quality decision is based must be designated as raw data.
Since usually the data itself is not changeable with the controls (SPS) and process control systems, one might also argue if necessary that no audit trail is carried out, because the data is not changeable. However, this argumentation must be proven by appropriate validation with the evidence of the raw data protected by proprietary formats or strong access protection. This means that there must be test cases that prove that this defined raw data cannot be changed accidentally or with simple effort.
For such systems that do not have an audit trail, the Aide Mémoire mentioned above points out that in exceptional cases, in the case of legacy systems without an audit trail, an SOP can be used, for example, to document the corresponding change in a logbook and have it verified by a second person. It should be noted here that only those systems are defined as legacy systems which were installed before Annex 11 (1992) came into force (see Aide-mémoire 07121202, page 28, serial no. 2.4.5.9). There is also the sentence: "First it has to be clarified whether data can be changed at all (e.g. electronic recorders). If no, no audit trail is required."
For systems where there is a simple audit trail, a report tool should be used to query based on the definition of the raw data. At least those entries should be displayed that belong to process values that are required for a quality decision. If the data, e.g. temperatures, are directly related to the batch release, it should be checked whether the associated audit trail must also be evaluated before the batch release. For systems that also record the reason for the change, groups can be sorted by reason and clusters can be recorded and evaluated by reason. The evaluation should always be prioritized according to the risk for the product and thus for the patient. In second instance then also accumulations of reasons can offer reason to question technical defects.
The laws and guidelines themselves do not allow the requirement for a technical audit trail to be deduced, which virtually covers all configurations with basic data and records them in the audit trail. There is a change control procedure for these processes. As a result, no reviews of this data are expected at this point.
It should be noted here that the guidelines always assume that values will be changed and that the initial entry will therefore only record who has entered it in the sense of a hand signal for paper documents. This distinction is very well described in Votum V11003. In section B, penultimate paragraph, it says: "Automatic logs of the user are suitable to replace a hand signal".
In order to meet the requirements of the audit trail review, further technical functions will be required in the future, such as configurable selection menus which allow selecting the reason for the change and providing standard reports and at least descriptive statistics.

7. Which person, e.g. in the laboratory, should perform the ATR?

Dr Wolfgang Schumacher
There are contradictory statements in the literature about the responsibility for conducting the audit trail review: While the current guidelines from the WHO, MHRA and PIC/S see the responsibility for the review in the department that generated the data, the FDA (in the final version of the guideline published in 2018) requires a review by the Quality Unit, i.e. quality assurance. Experts from industry and European authorities consider the FDA approach to be rather inappropriate, as the QA cannot ensure full detailed knowledge of all production and quality control processes. This applies especially to biotechnological processes.

8. Many production processes are documented on paper by means of manufacturing protocols. How does a review of the audit trail stand in relation to this? Should the good documentation practice in the manufacturing protocol be checked by means of an audit trail review?

Karl-Heinz Menges

If the documentation is done electronically, it is not clear in many cases whether a specific value is the original entry or whether changes have been made subsequently and how the changes were justified. In paper-based (manufacturing or test) records, changes must be made in such a way that the original entry remains legible and the change must be signed and dated; if this is not obvious, the reason for the change must be stated. (EU GMP Guidelines Chapter 4 No. 4.9) This allows the person who decides on the quality of a product or material to see whether subsequent changes exist and evaluate them. In the case of electronic documentation, an audit trail provides an equivalent to this information.

9. Annex 11 and other guidelines stipulate that the audit trail must be checked "regularly". However, is it really stipulated in some way that this must be done before the product is released?

Dr Wolfgang Schumacher
The regular check of the audit trail, which had been required since its publication in June 2011, was frequently questioned by representatives of the authorities at conferences and seminars. In all these discussions, the authorities rated the approval process for a pharmaceutical dosage form (final release for sale) as the most important process step of all, since no further reviews are carried out at a later time. Thus, the final steps determining quality are the inspection of the manufacturing protocol, the quality control protocol, the audit trail review and the implementation of the batch status from "quarantine" to "released" in the ERP system.

10. Audit trail review only for critical data: Does this mean that only systems with data that have a direct influence on the product can be audited? Not for systems with only an indirect influence?

Dr Wolfgang Schumacher
In deciding whether a review of the audit trail is required, several factors need to be considered: If it is not possible for the user to change/delete/supplement data after the initial entry, a review of the audit trail is not necessary. Furthermore, systems that only provide "subordinate" data for batch release (e.g. dimensions of a tablet) can be excluded from the audit trail review. The criteria for this must be recorded in a written data risk analysis.

6.4 Bioburden – Regulatory Expectations and Practical Experiences Q&As

1. Bioburden Testing

1.1 (i) "A limit of 10 CFU per 100 mL is generally accepted for bioburden before sterile filtration. Do you think that starting with a 100 mL sample and separately analyzing 50 mL on TSA medium and 50 mL on Sabouraud dextrose agar, then adding the two results, is an acceptable approach to provide a bioburden result for 100 mL? Are you aware of such an approach being used in the industry to reduce the amount of product used for QC testing?"

(ii) "Do you also consider splitting the sample in two aliquotes: one on TSA for TAMC and one on SDA for TYMC and summing both results? Would it be acceptable? For example, for a 10 mL sample, 5 mL would be used for TAMC & 5 mL for TYMC; if we find 3 cfu for TAMC and 2 cfu for TYMC, the total would be 5 cfu /10 mL sample size?"

(iii) "Sample amount for bioburden testing of APIs is usually 10g. Can the sample amount be reduced for cytotoxic APIs? Is there any need to start with this high amount? How this could be justified?"

For the membrane filtration method the description in Ph. Eur. 2.6.12 "Microbiological examination of non-sterile products: microbial enumeration tests" provides guidance in sections 5. TESTING OF PRODUCTS (see sub-section 5-1. AMOUNT USED FOR THE TEST and 5-2. EXAMINATION OF THE PRODUCT): "Unless otherwise prescribed, use 10 g or 10 mL of the product to be examined" and "[…] transfer the appropriate amount to each of 2 membrane filters and filter immediately. […] For the determination of TAMC, transfer one of the membrane filters to the surface of casein soya bean digest agar. For the determination of TYMC, transfer the other membrane to the surface of Sabouraud-dextrose agar."

This means that for a required or internally defined sample volume of 10 ml, 10 ml each must be tested for the TAMC and the TYMC. However, the Ph. Eur. describes the following exceptions: "For materials used as active substances where sample quantity is limited or batch size is extremely small (i.e. less than 1000 mL or 1000 g), the amount tested shall be 1 per cent of the batch unless a lesser amount is prescribed or justified and authorised. "For products where the total number of entities in a batch is less than 200 (e.g. samples used in clinical trials), the sample size may be reduced to 2 units, or 1 unit if the size is less than 100." (see 5. TESTING OF PRODUCTS, 5-1. AMOUNT USED FOR THE TEST).

It is recommended that sample volumes deviating from the cited specifications should be discussed upfront with the competent competent authorities and approved by the authority.

In the case of the bioburden determination before sterile filtration, the "EMA-Guideline on the sterilization of the medicinal product, active substance, excipient and primary container" gives guidance regarding volumes to be tested. Here it is stated, that 100 ml, should be tested for TAMC, while TYMC is not mentioned. It is generally accepted that only TAMC is tested, if the recovery of representative yeasts and molds can be shown during method suitability. The draft USP chapter <1119> also hints in this direction. The testing volume of 100 mL may also be reduced, if justified.

1.2 Is the action limit and the specification limit the same thing? For example, it is appropiate to set the action limit for WFI as 10 CFU/100 mL or 0.25 EU/mL?

No – the definitions in ICH Q6B are as follows:

- Specification: A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform to be considered acceptable for its intended use. "Conformance to specification" means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.
- Action limit: An internal (in-house) value used to assess the consistency of the process at less critical steps.

1.3 With the "Proposed Compendial Approach for the Implementation of Microbiological Examination of Nonsterile Products–Tests for Burkholderia Cepacia Complex (BCC)" is there any clarification on the expectation for water testing? In the current version the wording 'optional testing of water' is vague.

No Ph. Eur. Eur. monograph - neither in the water monographs nor in a product monograph – requires to demonstrate the absence of B. cepacia or organisms of the BCC. However, for certain products or classes of products, a contamination with B. cepacia or organisms of the BCC may pose a risk to patients. However, this must be defined on a product or product class-specific basis. In these cases, the absence of B. cepacia or organisms of the BCC in the final product must be demonstrated.

1.4 Bioburden Test performance (slide 14): it was explained that the TSA plates are incubated 5-7days at 25-30°C, but the UPS draft chapter writes the standard TAMC incubation for 3-5 days at 30-35°C. what is your strategy/rationale?

Ph. Eur. 2.6.12 and USP<61> are harmonized via the PDG and the ICH-process. In both pharmacopeias the requirements are as follows: "Incubate the plate of Soybean–Casein Digest Agar at 30° to 35° for 3 to 5 days and the plate of Sabouraud Dextrose Agar at 20° to 25° for 5 to 7 days."

Note: Other incubation regimes are accepted, if appropriately justified and validated.

1.5 Do you have a rational supporting the use of TSA only for bioburden test (by opposition to Eur. Ph.2.6.12 prescribing TSA and SDA)

Data were generated that show that the TAMC is suitable for detecting a wide range of aerobic microorganisms, including yeasts and fungi. These data have been discussed with numerous regulatory authorities worldwide. Based on these results, the regulatory authorities have approved the sole use of the TAMC for the microbial control of the biopharmaceutical production processes.

1.6 In practice, how do you manage a sample hold time exceedance? Do you generate data on microbial growth kinetics to support a risk assessment? If yes, how do you support the choice of microorganisms included in the study?

If a sample hold time is exceeded the sample is considered invalid, resulting in a "missing bioburden" event. If you are at risk of exceeding the hold time due to your planned process (e.g. external lab), you should validate a sufficient sample hold time upfront.

1.7 In Hold Time Consideration, do you also take into account the exposure to light?

No.

1.8 Do you validate a Cumulative Hold Time at large scale manufacturing?

No.

1.9 How many batches should be sampled for bioburden to establish production bulk holding time - e.g. holding time between start of compounding and end of 1st filtration?

Three batches.

1.10 Regulatory expectations related to bioburden data integrity. Second verifier analyst requirement for plate counting?

In theory, yes. For some bioburden sampling points the contemporaneous verification could be waived based on a risk assessment. Guidance for such a risk assessment provides BioPhorum's RISK ASSESSMENT OF TRADITIONAL CULTURE-BASED MICROBIOLOGICAL TESTS REQUIRING CONTEMPORANEOUS VERIFICATION. The current draft of the revision of USP <1117> follows this philosophy.

1.11 (i) "When the specification of the product has to be reported as combined TAMC and TYMC, should all colonies of each plate being counted, sum and reported regardless type of microorganism? I mean,
- TAMC: 1 bacteria and 1 Mold - 2 CFU/10 mL
- TYMC. 1 bacteria and 1 Mold - 2 CFU/10 mL
- Final result: Combined TAMC+TYMC: 4 CFU/10 mL?"
(ii) "What do you think about the sum of TYMC and TAMC results sometimes expected by EU inspectors?"

(iii) "You has TYMC in the past. How did you manage the results? TAMC and TYMC separatly compared to 10 CFU/100 ml? Or you made the sum of both (as expected by some authorities)?

Neither Roche nor Novartis perform a TYMC count. Hence, this aspect is irrelevant for us.

1.12 (i) "Is SDA required for monitoring each steps of the in the drug manufacturing process? OR TYMC specification is just required for product release?"
(ii) "Is TYMC really expected for in process bioburden testing for sterile products?"

Health authorities have accepted that we test all IPC levels and the Drug Substance using TAMC only.

1.13 (i) "What are the studies to perform to prove that TAMC is sufficient to recover the most probable MO in our environment?"
(ii) "Expose if they have develop tests to prove that most yeast and molds could be recovered on TSA in these incubation conditions?"
(iii) "Never any expectation to prove that any mold or yeast would grow on TSA in your incubation conditions?"

We did not perform any specific studies. Yeast and molds are included in our method suitability tests and these experiments and results were sufficient for the health authorities that we could waive the TYMC.

1.14 To recover yeast and molds on TSA should we modify the incubations conditions?

No - we incubate at 30 - 35 °C.

1.15 (i) "Did you somewhere demonstrate that the 24 hours shelf life of bioburden sample has no impact on the representativeness of the sample?"
(ii) "You said that the Bioburden Sample Hold Time of 24 hours was not always accepted. Could you share some examples?"

No - a shelf life of 24 hours was accepted by the health authorities without supporting experimental data.

1.16 (i) "For suitability / validation of IPC bioburden = how many local isolates used on how many different batches?"
(ii) "Which type and number of local strains do you add to the Growth Promotion Test?"

Two in-house isolates must be involved in the bioburden Method Suitability Test.

1.17 Specify the incubation conditions for TAMC: temperature and duration?

30-35°C for 3–5 days. Note: using a validated automated colony counter the incubation time is only 36 hours.

1.18 For bioburden filtration method, if no growth is detected, how the result should be reported as 0 CFU/10 mL or <1 CFU/10 mL for a sample with specification of ≤10 CFU/10mL?

You can report either 0 CFU/10 mL or <1 CFU/10 mL. Your internal test method must define the reporting.

1.19 Temperature 5°C is more important than time for bioburden...so what about an holding time of 48h max but keep at 5°C and without data? (note: explicit question to the Novartis colleague)

The sample hold time was discussed with numerous authorities and a 24-hour hold time was finally agreed upon. This sample hold time is described in the dossiers and accepted by the authorities.

1.20 Do you have retest samples for bioburden and how use it?

If the defined and filed shelf-life of the bioburden sample is exceeded (note: 24 hours) we do not have a valid sample anymore.

1.21 Hold time for DP release when sterility and LAL testing apply? 24 hours is requirement from sampling to testing, but is there any hold time restriction between filling and testing?

Typically, no sample hold time is defined for sterility test samples. An "endotoxin recovery study" should be performed to assess whether any sample-specific endotoxin masking effects requires defining a sample shelf life for endotoxin samples.

1.22 For phase III validation covering three batches (before commercial), can the IPC routine results be used for release when validation activities are ongoing? Or should the method validation covering all IPC steps be complete before routine IPC results can be used for release?

All validation efforts must be completed prior to the release of any material.

1.23 What is the rationale behind using In-house strains in Method Suitability Testing for Bioburden, which Sven (and others) mentioned? (note: explicit question to the Roche colleague)

The bioburden test method used should be able to detect microorganisms relevant for your manufacturing process and the respective facility / manufacturing environment. This will be demonstrated by including representative in-house isolates in your method suitability test.

2. Microbial Control System

2.1 (i) "What is the lower specification for a bioburden? A bioburden with specification less than 1 is not realistic? (due to the environment, consumables and equipment of the test)? So what should be the lower specification? Less than 3? Less than 5?"
(ii) "Regarding bioburden limits: Samples from BDS production in Class D, C and B are taken aseptically and analyzed in a non-classified microbiological laboratory. Occasionally, a couple of colonies can appear on plates from sampling or handling. Does it make sense to have a bioburden limit of <1 CFU/10 mL in this setting or what would you recommend?"

A stepwise progression of limits is defined. Tighter limits are set closer to the end of the process with ≤ 10 CFU/10 mL if DS is frozen.

2.2 (i) "Did you perform a bioburden method suitability test for each defined sampling points? Or did you adopt an approach based on a worst case sample (probability of the intermediate / buffer to interferes with the test) to cover some other steps and reduce method suitability test effort based on a risk assessment?"
(ii) "Authorities and inspectors - to what extend do they expect monitoring the control of bioburden in the complete buffer/drug substance/drug product process, is this all risk based?"

Yes, a Method Suitability Test is performed for each defined sampling point. A risk-based approach is used to define the sampling points considering e.g. amongst others (i) configuration of process equipment, including the placement of bioburden reduction filters to avoid possible blind spots in detection of contaminants or (ii) open processing steps and surrounding environment or (iii) the potential impact of conditioning steps (e.g., extreme pH adjustments or solvent/detergent additions)

for potential inactivation of putative bioburden must be considered or (iv) the growth-promoting capability of the process pool.

2.3 Should buffers which are received sterile filtered be tested for bioburden before being used in manufacturing? We already test for endotoxin.

There are no specifications that require this. If sterility of the buffer is mandatory, then this should also be verified by certificates or demonstrated by testing.

2.4 (i) "Should there be alert levels for all bioburden IPCs taken from aseptic production?" (ii) "For aseptic production in class C-D clean rooms, do you still recommend alert levels for all IPC steps? Or is alert levels for IPC steps only required when aseptic production in class A-B?"

Yes.

2.5 Can processes of pH manipulation of the pool (like viral inactivation) mask the presence of bioburden or endotoxins in it? I mean, is possible BB being detected in the BB analysis in a sample of the pool prior to execute the viral inactivation and not after the viral inactivation is ended?

Yes - the potential impact of conditioning steps (e.g., extreme pH adjustments or solvent/detergent additions) for potential inactivation of putative bioburden must be considered.

2.6 Do you always sample and test for endotoxins in parallel to Bioburden? If not why? (note: explicit question to the Novartis colleague)

Not always but in most cases. Note: EMA GUIDELINE ON THE STERILISATION OF THE MEDICINAL PRODUCT, ACTIVE SUBSTANCE, EXCIPIENT AND PRIMARY CONTAINER does not request to test for endotoxins prior to sterile filtration. Only a bioburden control is requested.

2.7 If alert levels are required for all IPC steps does it then apply to all product phases (Phase I-III, PPQ and commercial)? And how do you establish alert levels for phase I-III and PPQ if only a small amount of batches have been produced?

Yes. Provisional limits are used during development until sufficient historical data has been generated. Alternatively, for products manufactured infrequently (e.g. in development) data from similar processes may be used.

2.8 As the Bioburden is sampled before sterilization by filtration the product is not yet sterile so some inspectors want us to apply all expectations that are rather applicable to biological DS. Is this relevant? What would you recommend?

The philosophy of stepwise progression of the limits should be applied for DP manufacturing as well. Hence, the limits applied for Drug Product manufacturing should not be less stringent as the limits defined for Drug Substance. Stepwise progression of limits.

2.9 What about the bioburden (and its by-products) impact on used production equipment. In case of microbial counts; there is any guideline/rationale to assess resins/UFDF membranes safety to be used again in the manufacturing process? If the event is TNTC and no calculations can be performed, there is any way (e.g. some kind of blank run study) to defend no impact due to this by-product?

Cleaning and sanitizing operations should be stringent enough to remove contaminants and any by-products. The effectiveness of the cleaning and sanitizing measures must be proven in a cleaning validation and a monitoring of the cleaning and sanitizing measures must be established in the routine.

2.10 Regarding hold time limits for manufacturing, is it important to define hold times for each process step? Or the overall hold time (all process steps until start of sterilization) is what matters from a microbiological point of view?

Yes. A maximum hold time for each process step must be defined and validated.

2.11 You described controls to assess the risk of contamination for Pharmaceutical ingredients and API manufacturers. To your knowledge, is there a requirement for environmental monitoring of facilities manufacturing API or raw material intended to be used for the manufacturing of non-sterile drug product (dry forms)

If a hygiene zone is defined for the production in which the production is to take place, then the requirements for this hygiene zone must be fulfilled.

3. Drug Substance Manufacturing

3.1 Is it bioburden anaerobic test required or FDA expected in any of the manufacturing process steps, such us in cell culture?

Yes, FDA requested to test for anaerobic bioburden at the end of the mammalian cell culture process.

3.2 Was the mammalian cell culture media used in the final bulk of the product?

No. In CHO-based expression systems, the product is released into the supernatant. The supernatant is purified. Hence, the cell culture medium is no longer in the final product.

3.3 Question: "What is the recommended method for pre-culture harvest samples in order to microbial detection, filtration method or liquid media as TSB?"

It depends on the specification for the pre-harvest samples. If "absence of any microbial contaminations" is defined, a qualitative method such as the direct inoculation could be used. If a bioburden limit is defined – e.g. ≤ 10 CFU/10 mL – a quantitative method must be used. Due to the defined volume to be tested, only the membrane filtration method is applicable.

3.4 Question: "Referring pre-filtration samples of the column eluate. Elution phase is usual not constant during the whole phase, normally a high peak of concentrated product is eluted in the first fraction of the elution while the concentration of product lowers as the end of the phase is nearing. Which moment should be sampled and how we can assure that is representative of the whole phase?"

The bioburden in the relevant fraction used for further processing should be tested.

4. Drug Product / Final Product Manufacturing

4.1 (i) "EMA Guideline on the sterilization of the medicinal product, active substance, excipient and primary container (6 march 2019) states that "In most situations, a limit of NMT 10 CFU/100 ml (TAMC) would be acceptable for bioburden testing". From your perspective, does therefore 100 ml represent the minimal volume to be filtered? And do you have experienced FDA expectation about minimal volume for product to be filtered?"
(ii) "What is a reasonable bioburden limit prior to sterilization of a small volume pharmaceutical solution? Guidelines suggest 100 cfu/100 ml, but if the whole batch is only one vial of 20 ml, this would mean 2 cfu per vial, almost sterile. 100 cfu/100 ml does not make sense, but what other limits may be justified?"
(iii) "Is the specification/acceptance level 10 CFU/100 ml?"

A sample volume of 100 mL is expected. Any deviation from this sample volume must be justified and accepted by the competent Health Authority. Generally, no "minimum" volume can be defined. It is always a case-by-case consideration.

4.2 Question: "For terminally sterilised products, for which the manufacturing process includes a bioburden reduction filtration step before sterilization, where in the process should IPC bioburden be sampled? Is it OK to test bioburden after filtration (but before sterilization)? Or bioburden should be tested on the bulk (before filtration and sterilization)?"

Additional sampling points may be required if the Drug Product manufacturing process includes further process steps.

4.3 (i) "When analyzing a 10 ml sample (IPC or DS), do you express final result in CFU/10 ml or do you allow extrapolation to 100 ml to comply with EMA Guideline on the sterilization of the medicinal product, active substance, excipient and primary container (6 march 2019)?"
(ii) "Spec < 10 CFU/100 ml ... if we have only 10 ml to be test, then I found not comfortable to have a specification < 1 CFU/10 mL : The bioburden test made under microbiological lab can't manage a specification of < 1 (equipment, environment of the test...)?"
(iii) "For small size batches you are ok to extrapolate a result obtained on a 10 ml (or 30 ml) sample to 100 ml. This is based on an assumption that micro contamination is homogeneous in a sample. However, most of time, germ are clustered in a sample. Therefore how do you justify you approach?"
(iv) "What is the considered a low batch size? max 10 liters ? more?"

Your internal test method must define the reporting. The final result could be reported in CFU/10 mL or after extrapolation in CFU/100 mL.

4.4 (i) "Did you demonstrate Mycoplasma retention capability of your 0.2 micron-filter when used for sterilization of products?"
(ii) "Especially how did you manage USP<1229.17> chapter on mycoplasma sterilization? Or do you plan to go to a standard 0.1 micron sterilization?"
(iii) "Bioburden prior sterile filtration: do you check really absence of Mycoplasma?"

Yes (for DS process) and No (for DP process). Typically, the requirements for filter used for final sterile filtration provided in sub-section 4.1.5. "Sterile filtration" and the filter data to be provided in the quality dossier is summarized in Table 3. of the EMA guideline are used. Absence of Mollicutes will be demonstrated at the end of the cell culture / USP process and aseptic manufacturing conditions guarantee that no Mollicutes contaminations occur during the DSP process. (Note: USP chapters above 1000 are not binding but for information only).

4.5 Alert level = how is perform the identification? Always by 16S rDNA sequencing?

Yes.

4.6 Annex 1: Terminally sterilisation stated as bioburden might be monitored. So not as mandatory. What is your experience with inspections/authorisations regarding this topic? Was that the reason to go to batchwise testing, or was there another reason?

EMA Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container clearly requests monitoring of bioburden prior to the final sterilization process.

4.7 If the last Bioburden sample should be missed (due to lab error or other reason), would this immediately mean a rejection of batch, or could also then historical data save the batch? Or sterility testing of final product?

In principle, a missing bioburden result does not mean that the batch must be rejected. The company has the possibility to perform a risk assessment. If the bioburden result of a late IPC sample is missing

- or even the bioburden result prior to the sterile filtration step - then it will probably be very difficult to release the batch on the basis of a risk assessment. Ultimately, the QP decides in Europe and the QA unit in other countries.

5. Risk Assessment

5.1 Is the risk assessment of MO recovered in an in-process bioburden for a sterile product an expectation?

During the batch release process, each contamination event must be investigated as to whether it could have an impact on the product and/or patient safety and thus whether the batch concerned can be released or not on the basis of a risk assessment.

5.2 Do you consider that the risk assessment documentation scope also include In-process control bioburden test on manufacturing intermediates or buffers (for biopharma drug substance manufacturing)?

Yes

5.3 (i) "Could you share some steps for the non-bioburden procedure if test for bioburden is missed."
(ii) "When a bioburden result is missed do you handle this situation as a non conform bioburden result?"

An Investigation of Missing Bioburden Result is a cross-functional activity including QC, QA and Production.

- In a first step, the reason for the missing bioburden result must be identified and CAPAs must be defined.
- The next step is to evaluate the ability of the manufacturing process to remove the contamination and/or possible by products.

If available, the following data could be considered:

- Bioburden results for the process steps before and after each sample type
- Trend analysis and relevant bioburden results over the runs for the sample type in question
- Endotoxin results for the first process step in which this test is performed after the sample type in question
- Provide an assessment of environmental QC data for the production site and the Water used for process operations for the sample type in question.

5.4 Is patient safety and product quality assessment required for in-process test pre-filtration bioburden of sterile products?

No – the expectation is if the bioburden limit is exceeded the batch should be rejected.

5.5 For ID of bioburden >alert level, to what level to you perform identification (always to species-level, or Gram-characterization)?

16S rDNA sequencing is used as for the case-by-case assessment of bioburden excursion the contaminant must be identified to perform the next steps of the assessment.

5.6 Product Quality Impact (PQI) calculation. Is it taking into account the doubling time of the microorganism and the time from sampling until product pass through the filter to calculate the theoretical level of bioburden reached? And is this number use for the PQI calculation and not the bioburden count in the sample?

No, the bioburden count in the sample is the relevant value.

5.7 The critical components are analyzed in theory or really practical measures (with external contractors)?

It is a combination of literature review, experimental study (proteomic study) but also clinical studies.

5.8 Which stability tests are recommended for justified there is not PQI?

Assays that analyze the integrity of the product.

5.9 For the assessment of Bioburden Excursions, bacterial DNA and cellular components could potentially be released from all bacteria. This means that for these components the number of microorganisms in the IPC is used to calculate the risk (microbial ID does not matter in this case)?

For the fraction of e.g. flagellin or bacterial DNA we use generic values. However, for e.g. cell wall components, it makes a difference whether the contaminant is a Gram-positive or Gram-negative bacterium. Whether a contaminant produces exotoxins, and if so, which ones, can only be evaluated if the contaminant has been identified.

5.10 What are the key literature sources/references for the patient safety assessment? (note: explicit question to the Roche colleague)

An important document is the Registry of Toxic Effects of Chemical Substances (RTECS®), Comprehensive Guide to the RTECS, D. V. Sweet Ed., US Department of Health and Human Services, Public Health Service, 1997.

5.11 Literature search: do you find always the information about theoretical conc. of PAMPs?

Yes.

5.12 Proteases are evaluated during the PQI assessment right?

Yes.

5.13 If the result reported of the count is TNTC, is there any worst case to perform a PQI?

We do not use a generic assessment of bioburden excursions. The test method must be able to quantitate ≥ 10-fold the action limit. But theoretically, you could also do a calculation / an assessment assuming you have a contamination with 1000 CFU/mL or 10,000 CFU/mL of a worst-case microorganism. The model also works with such assumptions.

5.14 There is literature of more potent exotoxins with regards B. cereus, how do you determine B. cereus to be the worst case?

To our knowledge, botulinum toxins (produced by Clostridium botulinum) are the most potent bacterial toxins. Followed by tetanospasmin and tetanolysin (both from Clostridium tetani).

5.15 If the reduction of the bacterial by-products cannot be measured, we don´t know if the theoretical values calculated are reduce in the following process steps. Why is stability only recommended if there are not further reduction steps?

We know from process validation that cellular components (e.g. host cell DNA, host cell proteins, ...) are removed during the downstream process. However, we cannot define exactly what the purification rate is for specific microbiological components. Therefore, we only perform the stability study if in final purification process steps the bioburden value exceeds our pre-defined limits.

5.16 Is it safe to calculate the risk for each component separately? Maybe two components that both induce innate immune responses have synergistic effects? Or this is covered by the worst-worst-worst case aspect of the calculations?

For each component the calculation is a "worst-worst-worst"-case assumption. Hence, we negate synergistic effects. This is also accepted by the health authorities.

6. Raw Material / Direct Material Testing

6.1 What about testing of raw materials that should be used for sterile products, no testing of objectionable organisms is necessary for these raw materials?

For biopharmaceutical manufacturing processes, no objectionable organisms are specified. Except for direct materials where a monograph exists. These direct material must fulfil pharmacopeial requirements – and this could include the test for specified microorganisms.

6.2 For bioburden testing of primary packaging such as flexible bags, is it necessary to perform extraction efficiency test and to test the empty packaging for bioburden? Or you can reason that the microorganisms that gets extracted into the product is what matters and that they will be detected in the bioburden testing of the product (if you test bioburden pre-sterilisation on filled products)?

No testing of sterile single-use disposables is required. The manufacturer can accept the vendor's certificate (if all GMP-requirements are fulfilled, e.g. Quality Agreement exists, audits were performed, …).

6.3 Regarding Method Suitability Testing for Microbial Enumeration Tests when applied to Starting Materials. Should the hold time between adding the microbial suspension to the product solution and the filtration of the solution be quantified as a part of the MST? Should it be subjected to a Worst Case scenario or to an upper limit?

The method suitability test should reflect the bioburden testing under routine conditions. The method suitability test should be performed according to the relevant pharmacopeial General Chapter without any pre-incubation step after the addition of the spike microorganisms.