Pharmaceutical Quality Group

GOOD DISTRIBUTION PRACTICE

Guidance on interpretation and implementation

Pharmaceutical Quality Group Monograph No. 4

CQI Chartered Quality Institute

ECA Foundation
Fostering harmonisation of GMP/GDP regulations

GDP ASSOCIATION

GOOD DISTRIBUTION PRACTICE

Guidance on interpretation and implementation

A joint publication of the ECA Foundation and the Pharmaceutical Quality Group of the Chartered Quality Institute

Pharmaceutical Quality Group Monograph No. 4 (revised)

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The Pharmaceutical Quality Group shop at www.pqg.org
The member's area of the ECA Foundation's GDP Association website at www.good-distribution-practice-group.org

It is also available as a printed (A5 wire bound) version from:
The Pharmaceutical Quality Group shop at www.pqg.org

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General Introduction

The Pharmaceutical Quality Group

The Pharmaceutical Quality Group in the United Kingdom developed from a small group of pharmaceutical quality executives who met initially in 1977 to assist in the preparation of a supplier questionnaire for discussion at the 1978 seminar of the European Organisation for Quality Control. The group has expanded since that time and is now incorporated with the Chartered Quality Institute.

The objectives of the group are:
1. The open exchange of information and experience concerning pharmaceutical quality matters.
2. The development of a unified approach to pharmaceutical quality assurance and good manufacturing practices.
3. To promote and represent the status of pharmaceutical quality assurance professionals.
4. To promote education and training in the achievement of pharmaceutical quality.

The Pharmaceutical Quality Group initiated a project in 1983 with the intention of writing a series of monographs, the prime objective of which was to augment the published mandatory requirements of Good Manufacturing Practice by providing practical, comprehensive and non-mandatory guidelines. The target audience was identified as management and supervisory personnel engaged in the manufacture, supply and distribution of medicines, with particular emphasis on their future training and education.

The series of monographs currently contains the following titles:
1. Pharmaceutical Premises and Environment
2. Pharmaceutical Manufacturing (Processing and Packaging)
4. **Pharmaceutical Distribution**
5. Pharmaceutical Auditing
7. Pharmaceutical Contract Manufacture and Analysis
8. Pharmaceutical Documentation
9. Pharmaceutical Packaging Validation (produced jointly with The Packaging Society)
10. Cleaning Validation
11. Good Quality Control Laboratory Practice
12. Microbiological Control for Non-Sterile Pharmaceuticals (produced jointly with Pharmig)

Monograph 6 on Bulk Pharmaceutical Chemicals was withdrawn after the publication of ICH Q7 as EU GMP Part II. Monograph 3 on Elements and Philosophy of Pharmaceutical Quality Assurance is out of print.

About the ECA Foundation

The ECA Foundation was founded in 1999 as an independent not-for-profit organisation. It was set up to provide support to the Pharmaceutical Industry and Regulators to promote the move towards a harmonised set of GMP and regulatory guidelines by providing information and interpretation of new or updated guidances.
Today the ECA Foundation comprises a number of so-called interest and working groups. These groups focus on different GMP compliance aspects such as QP regulation, Validation, IT Compliance, Good Distribution Practice and other topics – and, for example, provide good practice papers which are intended to help industry and authorities to implement GMP in an effective manner.

In addition, the Foundation comprises the ECA Academy as its educational organisation. The Academy conducts a wealth of international education courses, webinars and conferences around GMP and regulatory compliance – picking up emerging GMP challenges and currently discussed subjects. Please visit www.eca-foundation.eu to learn more about the Foundation.

The European GDP Association

Established as an Interest Group of the ECA Foundation in March 2013, the objective of the GDP Group is to support all stakeholders involved in Good Distribution Practice (GDP) by providing them information about the implementation of GDP. In August 2016, the European GDP Group was reorganised to become the European GDP Association.

It is the goal of the Association to represent Responsible Persons for GDP, Logistic Managers and other individuals involved in a secure pharma supply chain. The Association provides its members with guidance documents on GDP interpretation, a discussion forum and a GDP Supplier Database. Membership in the European GDP Association is available at no cost. As a member of the Association, you will receive the latest information on Good Distribution Practices as well as information about the activities of the Advisory Board.

Please visit www.good-distribution-practice-group.org to learn more about the European GDP Association.

Other ECA Publications

- Audit Checklists:
  - PaaS Service Providers
  - SaaS Service Providers
- Code of Practice for the Responsible Person for GDP
- Good Practice Guides:
  - Duties, Responsibilities and Continuous Training for Qualified Persons in the EU
  - Validation
  - Visual Inspection of Medicinal Products for Parenteral Use
- Guidance Document: Data Governance and Data Integrity for GMP Regulated Facilities
- Laboratory Data Management Guidance: Out of Expectation (OOE) and Out of Trend (OOT) Results
- Standard Operating Procedures (SOP):
  - Laboratory Data Management – Out of Specification (OOS) Results
  - Selection Process for Cloud Service Providers

Foreword

Good Distribution Practice (GDP) requires that medicines are obtained from the licensed supply chain and are consistently stored, transported and handled under suitable conditions, as required by the EU Marketing Authorisation or product specification.
GDP is important, since getting it wrong can damage the product and potentially harm the patient. In getting it right you ensure that the right medicines, of the right quality get to the patient as intended and at the right time.

Increasingly, models for wholesaling and distributing medicines have become more complex; and as vulnerabilities in the supply chain are identified, regulations are enhanced to combat these. The most significant of these changes in recent times being those implemented with the advent of the Falsified Medicines Directive (2011/62/EU) in 2013, with further changes with respect to safety features to be implemented from February 2019 in the EU.

Pharmaceutical manufacturers, wholesalers and indeed regulators have needed to adapt over time to these changes. At the MHRA we identified a need to develop a dedicated GDP inspectorate in 2002, which has grown three-fold to today, which is commensurate with the growth of this business sector. We have also needed to adapt through developing different communications methods for different audiences utilising symposia, presentations, blogs and roadshows.

Through our risk based inspection programme we regularly identify sites where their understanding of regulatory compliance presents them with a challenge. I welcome this ECA PQG GDP Guideline, the outcome of significant work by a number of experienced professionals from across the EU, as it will no doubt assist in providing clarity and support for those operating with this sector.

Mark Birse
Deputy Director, Inspection, Enforcement & Standards Division
Head of Inspectorate
MHRA

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Combined volume

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Thanks to Denise Hosseiny and Sue Mann for their review and comments of the draft combined volume and for their assistance with the proof reading of this text prior to its publication.

Thanks also to Mark Birse (UK Medicines and Healthcare products Regulatory Agency) for providing the Foreword.

Preface

It is of key importance that medicinal products are not only made to a high quality in accordance with Good Manufacturing Practice, but that the quality and integrity of these products are maintained through the entire supply chain to the patient. This is where Good Distribution Practice (GDP) comes into play.

The distribution network for medicinal products is often complex, involving many different parties. In addition to the challenges associated with this complexity, there is also a growing threat from criminal activities seeking to introduce falsified medicines into the legal supply chain. Only through the sound application of GDP by all parties in the supply chain can we ensure that patients receive the quality medicines that they need.

Although the 2013 European GDP guideline provides far more detail than previous guidelines, it is clear from regulatory agency findings in recent years that there is a need for further guidance on the interpretation and implementation of the regulatory expectations, hence the creation of this monograph.

Both the PQG and ECA Foundation have similar aims in the provision of strong guidance on pharmaceutical quality-related topics and we have been pleased to facilitate this collaboration to the mutual benefit of all members and others involved in pharmaceutical distribution activities. The project began with the creation of a series of individual chapter guides to speed their availability, but it was always the intent to provide a single volume monograph and we are delighted that this is now complete. This would only have been possible with the input of experts drawn from the memberships of the PQG and ECA GDP Association and we would like to thank all those listed in the Acknowledgements section for providing their time and expertise.

Whilst this monograph is built around the format and text of the 2013 European GDP guideline, today's medicinal product supply chains are global, hence there is a need for GDP to be applied globally. The advice that follows will therefore be of universal benefit.

Regulatory requirements and expectations are not static and no published work can hope to be fully comprehensive. However, it is our belief that this volume will provide a sound basis for the implementation and maintenance of a GDP quality system with clear responsibilities and processes and the application of risk management principles. It should be of benefit to all involved in GDP activities for initial training, continuing professional development and as a reference source or audit tool.

We intend to revise this document periodically based on feedback from customers, so please provide any feedback and suggestions for improvement using the email address monographs@pqg.org or info@gmp-compliance.org.

Philip Butson, Afshin Hosseiny and **Ashley McCraight**
March 2018

Chapter 1 – Quality Management

1.1 Principle

Wholesale distributors must maintain a quality system setting out responsibilities, processes and risk management principles in relation to their activities(2). All distribution activities should be clearly defined and systematically reviewed. All critical steps of distribution processes and significant changes should be justified and, where relevant, validated. The quality system is the responsibility of the organisation's management and requires their leadership and active participation and should be supported by staff commitment.

(2) Article 80(h) of Directive 2001/83/EC

What is the rationale for this point of guidance?

A Quality Management System (QMS) defines a company's processes with a focus on meeting its customers' requirements and expectations. The purpose of this guidance is to ensure that the principles of Quality Management are understood and put into effect by pharmaceutical distributors. A QMS which details the activities relating to the storage and distribution of pharmaceuticals, in approved procedures and which sets out the responsibilities of personnel and management will ensure that patients receive safe and effective medicines in a timely manner.

What are the benefits and risks associated with this point of guidance?

A structured approach to managing quality through a QMS, involves the definition of critical processes and the identification of the critical aspects of those processes. Knowledge of the processes enables management to define responsibility and to assign adequate resources for each activity. A QMS is a management tool which, when used correctly, will increase the efficiency of a company and will save costs by reducing waste. It will also provide for the secure distribution of pharmaceutical products, ensuring that only legitimate pharmaceuticals may enter the supply chain and be delivered to the end user.

Implementation

- Develop a process map of the company's critical activities
- Define the critical point for each activity
- Define the responsibilities relevant to each activity
- Define the controls for each critical point
- Document the process in a detailed procedure.

The implementation of the QMS should be led by the organisation's management and include:

- Training of all personnel in appropriate procedures

- Encouragement of feedback from personnel to identify improvement opportunities
- Reviews of its effectiveness at regular, pre-determined intervals

Process mapping can be basic; simply displaying the process in a single dimension and detailing the sequence of activities or can be more detailed and include responsibilities for each of the process steps, along with the references to other procedures etc. When creating your process map:

- Identify the start and end of your process;
- Create a list of the steps within your process and then place these in sequence;
- Use appropriate symbols to identify the inputs to the process, the process steps themselves, the process outputs, the controls and the feedback/ communication pathways.

An example is given as Figure 1. It can also be useful to map complex supply chains as exemplified in Figure 2.

Further information relating to Quality Management Systems can be found in ISO 9004 and Eudralex Volume 4, Part III/ICH Q9 Quality Risk Management

1.2 Quality Management

The system for managing quality should encompass the organisational structure, procedures, processes and resources, as well as the activities necessary to ensure confidence that the product delivered, maintains its quality and integrity and remains within the legal supply chain during storage and/or transportation.

What is the rationale for this point of guidance?

A defined process for managing the QMS will provide appropriate tools for the company to manage their quality related activities, in order to ensure and secure a supply of products to their customers. The QMS should ensure, through appropriate procedures, processes, organisational structures and resources that products delivered and ultimately administered to patients will still retain their quality attributes. The QMS should also ensure that the product, is, at all times, handled, stored and transported within the legal supply chain.

What are the benefits and risks associated with this point of guidance?

Without a defined QMS, the company runs the risk of wasting resources, losing control of operations and potentially impacting the product quality and security of supply to its customers. If a company's QMS is not fit for purpose, this may increase the risk of illegal introduction of falsified medicine into the legitimate supply chain.

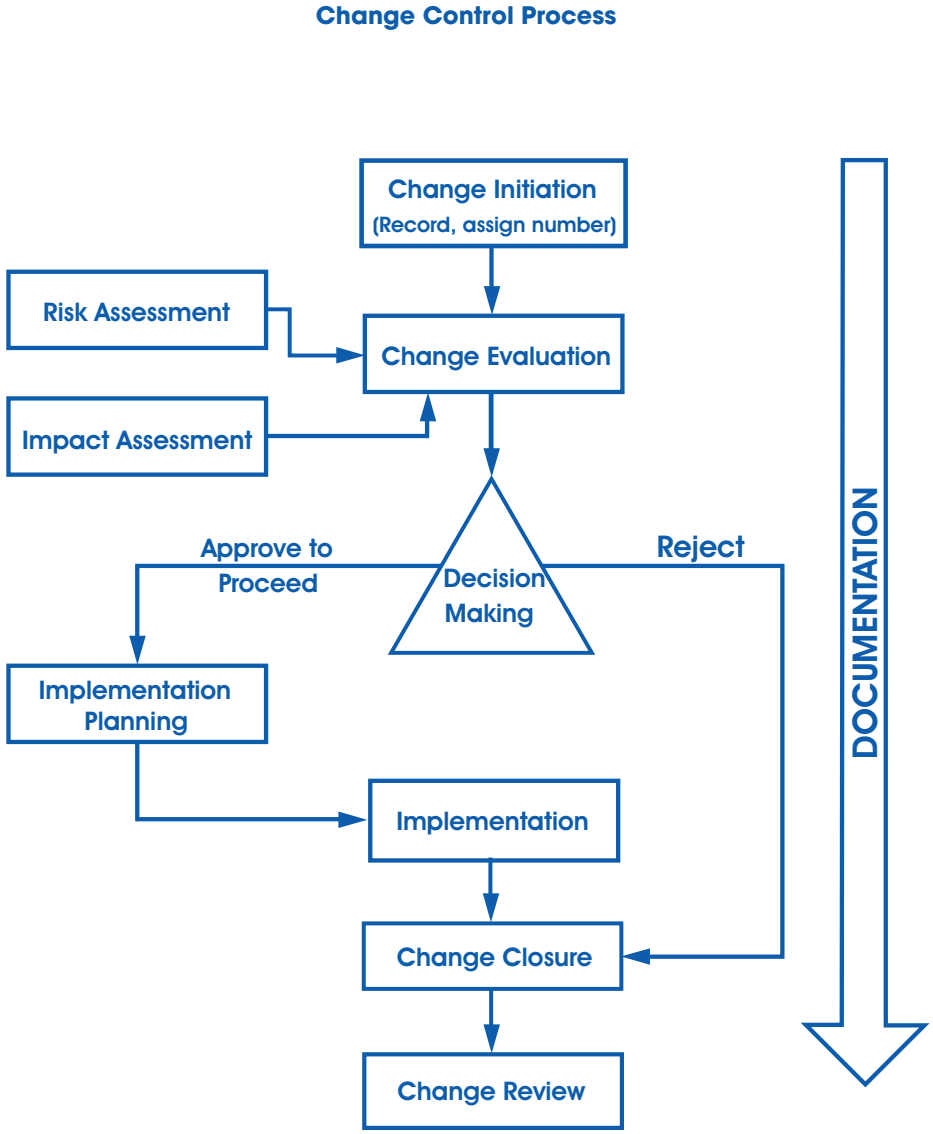

Figure 1: An example of a process map – a change control process

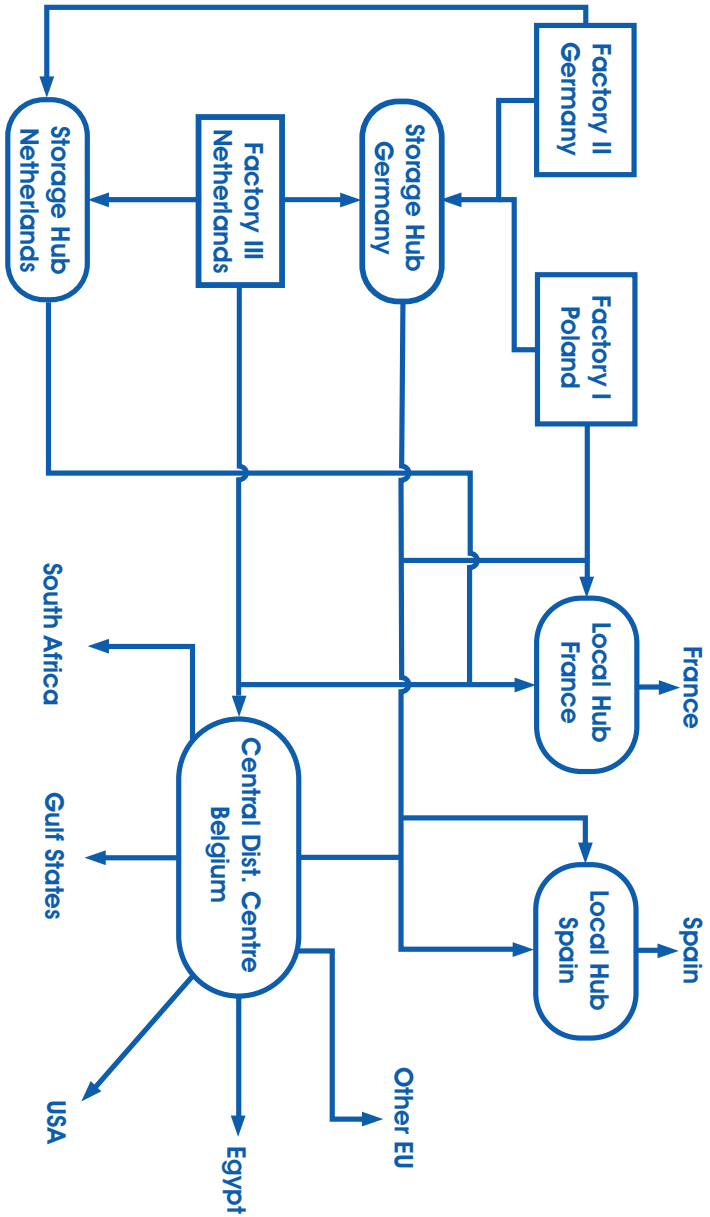

Figure 2: An example of a supply chain map

Implementation

- Draw the company's organisation chart – include a version number;
- Ensure key personnel (Quality Manager, Warehouse Manager, and Responsible Person) have job descriptions in line with the organisation structure;
- Allocate sufficient resource to each activity;
- Develop a detailed plan for training, based on role requirements.

1.2 Quality Management

The quality system should be fully documented and its effectiveness monitored. All quality system-related activities should be defined and documented. A quality manual or equivalent documentation approach should be established.

What is the rationale for this point of guidance?

A quality manual draws together all of the elements of the quality system into a controlled document, ensuring that the same management approved procedures are readily accessible to all staff. These procedures should ensure that the effectiveness of the QMS is routinely monitored and appropriate actions taken to ensure effective delivery of operational activities.

What are the benefits and risks associated with this point of guidance?

By outlining adequate quality systems within its QMS, a business can ensure that it remains efficient and compliant, routinely delivers the expected service to its customers and provides clear expectations to its suppliers. The QMS brings clarity to the operations, reducing the risk of errors and therefore reducing the time and resource required to investigate and rectify those errors, whilst maintaining customer satisfaction.

Implementation

- A fully documented Quality Manual should be established within the company document management system;
- Appropriate key performance indicators (KPIs) relating to critical activities and to the performance of the QMS should be defined in the Quality Manual;
- Requirements for monitoring of KPIs should also be defined in the Quality Manual and reflected in individual SOPs.

A Quality Manual contains the description of the quality system and should include:

- The quality policy;
- The scope of the quality system;
- Identification of the quality system processes, as well as their sequences and interdependencies;
- Process maps and flow charts to facilitate visualisation of quality system processes;
- Responsibilities of management within the quality system.

Guidance on preparation of the Quality Manual and of general quality systems can be found in ISO 9004.

Figure 3 provides a diagrammatic representation of how a Quality Manual might be organised to incorporate the different elements of the EU GDP Guideline.

The Quality Planning and Continuous Improvement cycle is represented in Figure 4.

1.2 Quality Management

A responsible person should be appointed by the management who should have clearly specified authority and responsibility for ensuring that a quality system is implemented and maintained.

What is the rationale for this point of guidance?

It is important that one person (normally termed the Responsible Person (RP)), be identified to take responsibility for ensuring that the quality system is up to date and reflective of current practice, and of regulatory and legislative expectations (see section 2.2).

What are the benefits and risks associated with this point of guidance?

The benefits to the company will include:

- Assurance of continued compliance with the regulations and best practices for maintenance of the quality system;
- Ensuring, via the RP, that procedures, processes, organisational structures and resources are implemented and kept up to date with the current regulations and business structure.

Patients will benefit from assurance that the products administered to them retain their quality attributes.

Implementation

- Identify and appoint an appropriately qualified individual (e.g., RP) as described in section 2.2;
- Ensure that this person be given authority and senior management support, appropriate to their responsibility for implementation and maintenance of the quality system;
- Document the role and responsibilities of the RP within the QMS. This job description should be signed and dated by both the RP and a management representative;
- Review the RP's job description routinely and update as required to ensure continued currency.

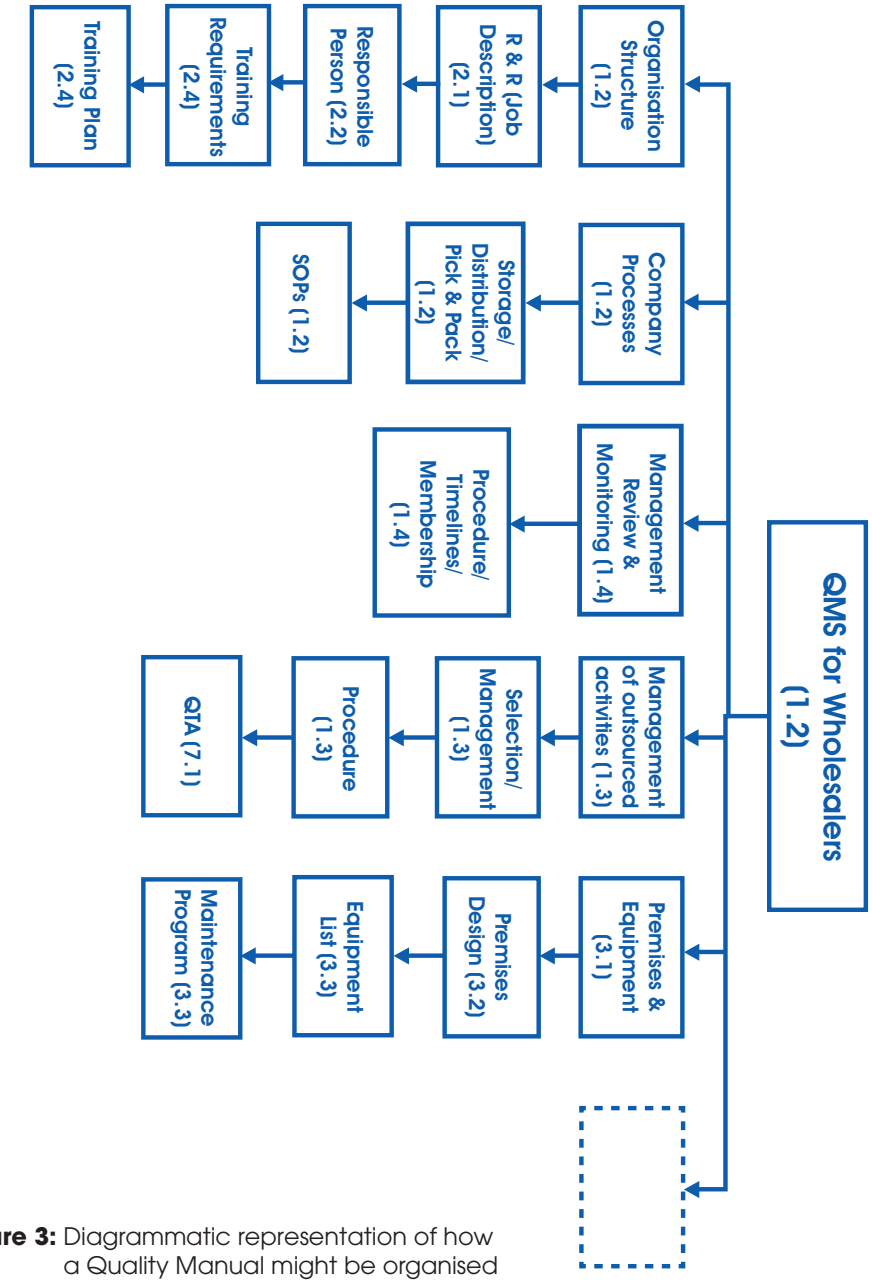

Figure 3: Diagrammatic representation of how a Quality Manual might be organised

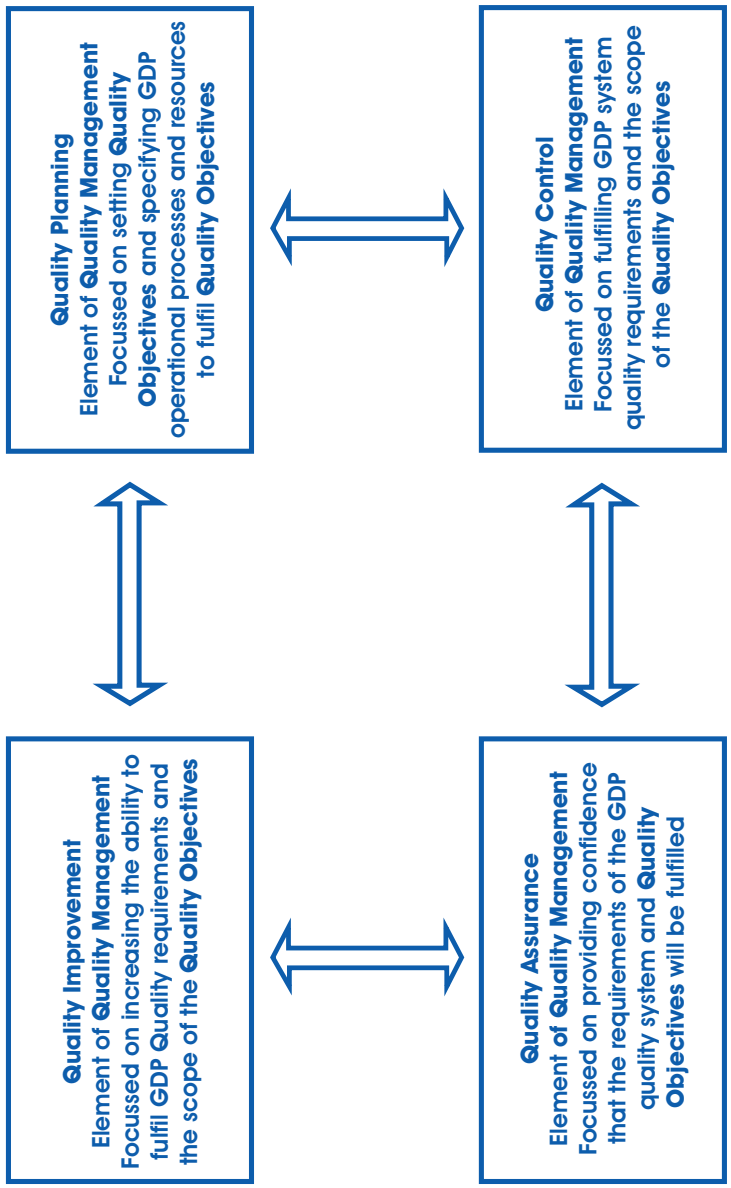

Figure 4: The Quality Planning and Continuous Improvement cycle

1.2 Quality Management

The size, structure and complexity of distributor's activities should be taken into consideration when developing or modifying the quality system.

What is the rationale for this point of guidance?
The QMS for the company should be fit for purpose. A smaller operation will typically have less complexity, allowing for a simpler QMS; a more complex operation will require a more complex QMS.

Whenever the company expands either the size or complexity of its operations, the management should review the QMS to ensure that it is still capable of controlling the expanded operations. If a potential risk is identified, then the QMS should be modified to minimise the impact of that risk.

What are the benefits and risks associated with this point of guidance?
The company can benefit from accurately identifying resource requirements and applying appropriate resources to each area. A QMS which has evolved to reflect the specific activities of the company will be much easier to implement, and maintain; streamlining training requirements and avoiding resource wastage.

Implementation
Applying the basic principles described earlier in this chapter, a company may develop an adequate QMS suitable for their operations.

1.2 Quality Management

A change control system should be in place. This system should incorporate quality risk management principles, and be proportionate and effective.

What is the rationale for this point of guidance?
The purpose of this is to ensure that all changes are properly evaluated, that their impact on the operations is formally assessed in order to avoid unexpected consequences before implementation. A documented change control system will allow for traceability of the changes, ensuring the QMS remains current and relevant.

What are the benefits and risks associated with this point of guidance?
The benefits of change control include assurance that changes made to the systems, facilities or equipment will not produce negative effects which result in costly mistakes or adversely impact on product quality. Good documentation of changes facilitates future reviews.

Implementation

- Prepare a detailed procedure defining what is classed as a change and how to proceed to initiate, evaluate and approve/reject a change proposal;
- Introduce a change control initiation form, or an electronic system to log the change proposal;
- Define the change review responsibility (depending on the nature of the change). E.g., a quality related change should always be reviewed by the QA/RP, whereas a safety related change may only be reviewed by the safety manager;
- Apply principles of risk assessment for review and approval of initiated changes (see ICHQ9). Changes should also be considered in relation to the potential impacts on regulatory requirements, customer Quality Agreements, validation status, and personnel training;
- Document all changes initiated in accordance with the change control and CAPA procedure;
- Ensure all changes are reviewed for effectiveness.

An example of a high risk situation might be a change in a temperature monitoring process where you would expect retraining of all users would be performed before implementation.

An example of a low risk change, which would require no special action, is a change that is made to a spelling in a procedure.

Most regulatory guidance regarding change management is currently found within texts relating to validation. However, the principles from the following texts are more widely applicable to change management as part of the quality management system. See, for example, WHO Technical Report series no. 937, EU GMP guidelines, Part I annex 15, ICH Q7, ICH Q9, ICH Q10, PIC/S Recommendations PI 006-3.

1.2 Quality Management

The quality system should ensure that:

(i) medicinal products are procured, held, supplied or exported in a way that is compliant with the requirements of GDP;
(ii) management responsibilities are clearly specified;
(iii) products are delivered to the right recipients within a satisfactory time period;
(iv) records are made contemporaneously;
(v) deviations from established procedures are documented and investigated;
(vi) appropriate corrective and preventive actions (commonly known as CAPA) are taken to correct deviations and prevent them in line with the principles of quality risk management

What is the rationale for this point of guidance?

This section provides more detail regarding specific elements that need to be built into the QMS.

What are the benefits and risks associated with this point of guidance?

See earlier coverage on this section.

Implementation

(i) See Chapter 5 – Operations – for details relating to procurement, storage, supply and export.
(ii) Define the responsibilities of management and other key personnel in written job descriptions agreed (signed) by both employee and manager. See Section 1.4 regarding management responsibilities in relation to review and monitoring of operations and Chapter 2 – Personnel.
(iii) See Section 5.8 – Supply – for how to ensure products are delivered as required.
(iv) See Chapter 4 – Documentation – for good documentation practices, including contemporaneous recording.
(v) Establish a deviation system to evaluate the impact of departures from defined procedures. Deviations should be documented in real time and investigated promptly. Risk assess the situation and use root cause analysis tools to establish why the deviation occurred so that appropriate corrective and preventive actions (CAPA) can be taken (see point (vi) below). Remember that deviations may have multiple causes. Include an analysis of any previous occurrences of the same deviation and whether previous CAPA have been ineffective.
(vi) Implement a CAPA management system to complement the deviation, complaint (see Section 6.2) and self-inspection (see Chapter 8) management systems. Its purpose is to ensure that appropriate actions are taken to:
   a. Prevent recurrence – Implement corrective action(s) to eliminate the cause(s) of a detected non-conformity or other undesirable situation.
   b. Prevent occurrence – Implement preventive action(s) to eliminate the cause(s) of potential non-conformities or other undesirable potential situations.

Features of the CAPA management system should include:

- Risk management principles to ensure that actions taken are focussed on the safety of the patient, and commensurate with risk;
- Documentation of each CAPA including:
  - Clarity regarding the action(s) required to close it;
  - An individual named as responsible for it;
  - An agreed reasonable due date;

- Approval by the RP or quality team.
- A log to enable tracking
- Regular management review to ensure timely progression and to identify any adverse trends, with action taken to address if required.

Further information on CAPA may be found in ICH Q10 or the Global Harmonization Task Force guidance.

1.3. Management of outsourced activities

The quality system should extend to the control and review of any outsourced activities related to the procurement, holding, supply or export of medicinal products. These processes should incorporate quality risk management and include:

(i) assessing the suitability and competence of the Contract Acceptor to carry out the activity and checking authorisation status, if required;
(ii) defining the responsibilities and communication processes for the quality-related activities of the parties involved;
(iii) Monitoring and review of the performance of the Contract Acceptor, and the identification and implementation of any required improvements on a regular basis.

What is the rationale for this point of guidance?

When an activity is outsourced, the contract giver remains responsible for ensuring that it is carried out correctly, but does not have direct operational control. Management of outsourced activities is necessary to provide assurance that these activities will be conducted as required and should therefore be part of the quality system. It is essential that the contract acceptor is both technically competent and legally able to undertake the required activities. To avoid any misunderstanding or uncertainty regarding requirements and responsibilities, there needs to be a written agreement between the parties and on-going communication processes. The contract acceptor needs to exercise oversight to ensure the ongoing suitability of the contractor's performance and act to address matters if this is not the case.

What are the benefits and risks associated with this point of guidance?

See Chapter 7.

Implementation

See Chapter 7.

1.4. Management review and monitoring

The management should have a formal process for reviewing the quality system on a periodic basis. The review should include:

(i) measurement of the achievement of quality system objectives;
(ii) assessment of performance indicators that can be used to monitor the effectiveness of processes within the quality system, such as complaints, deviations, CAPA, changes to processes; feedback on outsourced activities; self-assessment processes including risk assessments and audits; and external assessments such as inspections, findings and customer audits;
(iii) emerging regulations, guidance and quality issues that can impact the Quality Management System;
(iv) innovations that might enhance the quality system;
(v) Changes in business environment and objectives.

The outcome of each management review of the quality system should be documented in a timely manner and effectively communicated internally.

What is the rationale for this point of guidance?

The QMS is a management tool enabling the business to operate in line with the regulatory, customer and business expectations. The management team should therefore review the QMS to ensure it remains current and effective.

What are the benefits and risks associated with this point of guidance?

The benefits of implementing Management Review and a monitoring process include:

(i) Continuous identification of improvements to the QMS, operational processes and procedures to help maintain quality and compliance
(ii) Ensuring the appropriate resources are in place, that possibilities for innovation can be discussed and resources planned and made available as required
(iii) Ensuring the QMS is in line with the business and the regulatory environment and objectives on an on-going basis
(iv) Minimising risk to the business and customer by remaining current
(v) Improving efficiency by reducing waste

The risk is that without such reviews, emerging issues may not be identified and flagged to management in a timely manner, resulting in non-compliance issues and risk to product quality or security of supply.

Implementation

Depending on the size of the organisation develop a structured and formalised process for conducting routine, formal reviews.

On a regular basis (typically every 3 months), the outputs from the QMS should be discussed by the senior management team. These outputs would include but are not limited to trends of:

- Complaints;
- Deviations;

- Self-inspection findings;
- External audit inspection findings including regulatory authority inspections;
- Change controls;
- CAPA;
- Risk Assessments.
- Changes to legislation and/or guidelines and potential impact on the organisation

Minutes should be taken during the meeting including the points discussed, the decisions taken or actions to be taken, timelines and responsibilities. These should be shared with all relevant stakeholders and retained for reference. Actions should be managed (the CAPA system may be used for this).

It is useful to define within the procedure for conducting Management Review:

- The management team (by title, e.g., Responsible Person, QA Manager, Operations Manager);
- The required attendees (by title) for the meeting to go ahead;
- The required inputs and resources to ensure the review meeting runs efficiently – KPIs, audit reports, previous agenda items and follow up activities and timeline details.

ISO 9001 and ISO 9004 may be useful references.

1.5. Quality risk management

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of medicinal products. It can be applied both proactively and retrospectively.

Quality risk management should ensure that the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient. The level of effort, formality and documentation of the process should be commensurate with the level of risk. Examples of the processes and applications of quality risk management can be found in guideline Q9 of the International Conference on Harmonisation (ICH).

What is the rationale for this point of guidance?

Quality Risk Management (QRM) introduces the opportunity to understand potential risks in operations and to put into place measures to reduce and/or to control risks that cannot be removed. This structured approach will enable distributors to minimise the potential for adverse quality impacts relating to their business operations or to the medicinal products they are handling. Such impacts can be costly in terms of time and resources.

What are the benefits and risks associated with this point of guidance?

Benefits

- A structured approach helps to identify potential problems, which may otherwise not have been considered, allowing preventive actions to avoid the costs associated with failure;
- Prompts evaluation of the adequacy of controls currently in place or required to be implemented, i.e., identifies the vulnerabilities in the storage and distribution operation;
- Can potentially improve the process, e.g., numerous checks may be in place but may not be effective; these can be replaced by checks that are directly associated with the quality risks to the business;
- Can streamline processes, thereby achieving time and cost savings.
- Make processes more efficient.

Risks

- Wasted resources if the focus on the high risk areas of the business is not maintained.

Implementation

- Have a procedure (SOP) for QRM and ensure that it covers the four ICH Q9 elements of:
  - Assessment;
  - Reduction & Control;
  - Communication, and
  - Review.
- Select personnel for formal training in risk assessment methodologies and involve them to facilitate the conduct of risk assessments;
- Select personnel with relevant knowledge and experience of the activities being assessed to provide input to each risk assessment;
- Dedicate time to systematically work through the various elements of your distribution operations;
- Rank the risks within your operations and focus on those with highest risk first;
- Perform prospective risk assessments on all critical areas of distribution operations and any significant proposed changes to the activities;
- Document the outcomes of QRM activities;
- Identify actions required to reduce (mitigate) risks identified and feed these into the CAPA system;
- Communicate the risks and the control measures to stakeholders;
- Perform after action reviews following each set of assessments and refine the QRM process;
- Ensure outsourced activities are included in the process.

Chapter 2 – Personnel

2.1 Principle

The correct distribution of medicinal products relies on people. For this reason there must be sufficient competent personnel to carry out all the tasks for which the wholesale distributor is responsible. Individual responsibilities should be clearly understood by all staff and be recorded.

What is the rationale for this point of guidance?

Most supply chains are complex. Despite increasing use of computerised systems, people continue to be involved at all stages of the distribution process. People can have an adverse effect on activities if they are unaware of GDP requirements and how to behave accordingly. We rely heavily on people to perform numerous tasks correctly, including checking, recording, picking, transporting and delivering medicinal products. There is also reliance on people to respond appropriately to information that they receive that may affect product quality, so it is important that they are appropriately trained and competent.

What are the benefits and risks associated with this point of guidance?

Benefits

- Properly trained staff will understand the procedures they are tasked to complete and how their actions might affect product quality or security of supply. They will respond appropriately to time and workload pressures, avoiding the risks cited below.

Risks

- Insufficient staff may result in taking short cuts in operations leading to errors and risks to the medicinal products;
- Lack of training may lead to operators making mistakes resulting in waste, delays and product spoilage;
- Increased number of errors may result in customer complaints, reduce efficiency and increase waste;
- Regulatory censure.

Note that the organisation may appear to function satisfactorily for some time with these deficiencies only becoming apparent when the system is 'stressed', e.g., the workload increases or a significant event, such as a recall, occurs.

Implementation

- Use process mapping (see Chapter 1) to assist in identifying the tasks involved and the number of staff and amount of training required in each case;
- Develop a customised training plan for each role;
- Implement recruitment practices which will ensure that appropriately educated and, where relevant, experienced personnel are recruited;
- Customise the training plan to each individual's prior knowledge and experience;
- Ensure all staff, whether they work on or off site (including drivers), fully understand their role and receive adequate training prior starting to perform their assigned tasks;
- Extend training to temporary staff.

2.2 Responsible Person

The wholesale distributor must designate a person as responsible person. The responsible person should meet the qualifications and all conditions provided for by the legislation of the Member State concerned[1]. A degree in pharmacy is desirable. The responsible person should have appropriate competence and experience as well as knowledge of and training in GDP.

(1) Article 79(b) of Directive 2001/83/EC

What is the rationale for this point of guidance?

The wholesaling, storage and distribution of medicinal products is subject to strict legislation which covers all aspects of wholesaling activities. Therefore, it is essential for the companies to have services of a person who is conversant in the legislation and able to implement and oversee the requirements.

What are the benefits and risks associated with this point of guidance?

Benefits

The knowledge of the RP will help ensure that GDP requirements are met, thus ensuring the product is distributed to patients in good condition, in addition to meeting a fundamental requirement of the wholesale licence.

Risks

- Appointment of an RP is a licencing requirement for wholesalers, therefore without an RP a wholesaler is not compliant with legislation and risks losing its licence to operate;
- Without a knowledgeable RP in place, the company risks not implementing all the GDP requirements and becoming out of compliance with the legislation, which could impact product quality and risk to patient safety.

Implementation

The appointment of a RP should be carefully considered. This appointment is dependent on the size of the organisation, the complexity of the services and the product classes involved. In a small organisation with a small number

of product lines, it is acceptable for the licence holder to be the RP, or a part time contract RP may be appointed (as long as they meet the requirements in the Member State concerned). In a large multi-site wholesale distributor, a dedicated RP independent from the daily operations would be required, as well as having defined delegated duties.

The nominated Responsible Person should be able to show an in-depth understanding of medicinal products and should be able to demonstrate knowledge of GDP. Some key areas of knowledge and experience are listed below:

Knowledge

- Storage conditions/requirements for different types of pharmaceutical product;
- Basic understanding of degradation pathways and stability profiles of pharmaceutical products;
- GDP legislation and relevant guidance;
- Requirements for storage facilities, temperature control and monitoring programmes, including mapping and qualification;
- Quality Management Systems and how to manage these effectively;
- Handling of returns/complaints/recalls;
- Bona Fide checks;
- Risks associated with Falsified Medicines;
- Expectations of a robust Technical (Quality) Agreement with any sub-contractors;
- Controlled Drug legislation and requirements of the relevant Member State(s);
- Trained auditor.

Experience

- Experience of picking /packing procedures and FEFO (First Expiry, First Out) principles;
- Handling complaints and customer queries;
- Active involvement in GDP regulatory inspections;
- Audited internally to monitor the QMS and preferably also external audits covering the various stages in the distribution process;
- Supplier and Customer approval process;
- Creating/maintaining/auditing the documentation and records involved to ensure compliance with GDP.

Competent Authorities will assess the experience of individuals proposed as RPs. An RP is unlikely to be accepted unless they have a minimum of one year's experience of distribution activities. A longer period of experience, ideally in a management role, would be preferred.

Contract RPs

Contract RPs should have the same level of knowledge and training in company products and procedures as a permanent RP. This provides a practical limit on the number of licences that an RP can effectively support.

Licence holders should ask potential contract RPs about other licence commitments and be satisfied that they will be able to devote sufficient time to the proposed additional responsibilities. It should be noted that Competent Authorities have refused RPs being named on what they consider to be too many licences. The contract RP should also consider carefully if they can fulfil these professional responsibilities for another company.

See the COGENT RP Gold Standard and ECA Code of Practice for RPs.

The responsible person should fulfil their responsibilities personally and should be continuously contactable. The responsible person may delegate duties but not responsibilities.

What is the rationale for this point of guidance?

Some key activities that wholesalers perform require input from the RP, for example when executing a product recall, or authorising emergency supply of medicinal products (out of hours). It is therefore important for the RP be available when required.

What are the benefits and risks associated with this point of guidance?

Benefits

Having a RP or a deputy contactable at all times helps ensure effective management of operations and any incidents that may occur. Having a deputy RP also provides a good basis for succession planning within an organisation.

Risks

If an RP is not available to manage incidents, then decisions made by others may not be in line with the GDP requirements and could compromise patient safety and the company's licence for which the RP is legally accountable.

Implementation

- Nominate a deputy and add to the licence;
- Issue a formal job description for the RP and his/her deputy;
- Train deputy in the defined role, including GDP and ensure training is documented;
- Involve the deputy regularly in RP activities including audits;
- Create a contact list to include telephone number for the RP and deputy,

and the company's Managing Director, Marketing Manager and other senior management as appropriate;
- Ensure the RP can access company's electronic systems remotely;
- A contract RP can help provide an appropriate service as appropriate for the organisation.

The written job description of the responsible person should define their authority to take decisions with regard to their responsibilities. The wholesale distributor should give the responsible person the defined authority, resources and responsibility needed to fulfil their duties.

What is the rationale for this point of guidance?
The role of the RP is a vital position within a wholesale distributor, and therefore it is important to define the role, its responsibilities and the level of authority it carries to avoid any confusion.

What are the benefits and risks associated with this point of guidance?

Benefits
Providing the RP with a written definition of their role and responsibilities allows both the wholesale distributor's senior management and the RP to understand the expectations of the role.

Risks
- Without the roles and responsibilities of the RP being defined, key GDP tasks and activities may not be performed, or adequately reviewed;
- The wholesale distributor might think that the RP is dealing with a required activity, whereas the RP thinks that it is being done by another member of the organisation, leading to gaps in the wholesale distributor's compliance with GDP;
- In the event of a contract RP not having a job description it is more likely that gaps in compliance will occur, and could put both the RP and the company at risk;
- Lack of authority for RP may result in some key quality decision being made without consulting the RP.

Implementation
The job description of the RP should list the responsibilities detailed in the GDP Guidance, plus any other company specific activities assigned to them. A copy of the company organisation chart could be added to the job description to show where the role fits within the management structure of the wholesale distributor, with a list of what decision making authority the RP has without needing board or senior management approval.

The RP's job description should be reviewed and updated whenever changes in the nature of the business occur or changes to the licence are made.

In order for the RP to fulfil their duties and responsibilities, appropriate resources should be provided by the wholesale distributor. The level of resource required will depend on the size and complexity of the wholesale distributor and the activities being undertaken. Elements to consider for this analysis would be:

Activities
- Procurement;
- Selling;
- Storage;
- Distribution (in house or sub-contracted);
- Import / Parallel Import;
- Export;
- Returns.

Products
- Product portfolio (number of products handled);
- Product volume (quantity of products handled);
- Product categories (POM, P, GSL, Cold Chain, Controlled Drugs);
- Product classes (sterile/non-sterile, liquid/semi-solid/solid, medical gases);
- Unlicensed Medicinal Products / Specials.

Sites
- Number of sites;
- Types of site (Distribution only, Storage and Handling).

The responsible person should carry out their duties in such a way as to ensure that the wholesale distributor can demonstrate GDP compliance and that public service obligations are met.

What is the rationale for this point of guidance?
Compliance with GDP is a basic licensing requirement for wholesalers. As the RP is appointed to ensure the company remains in compliance with GDP requirements, it is imperative for the RP to be able to demonstrate that this has been achieved.

What are the benefits and risks associated with this point of guidance?

Benefits
Documenting activities is essential to GDP compliance but it also provides a clear audit trail of the activities undertaken, when they were undertaken and by whom. As well as providing suitable evidence that an activity took place at a particular point in time, documented records are very useful for conducting investigations into deviations and for performing root cause analysis.

Risks
Not documenting activities undertaken could result in lack of traceability, inability to perform investigations and learn from previous mistakes. The company will not be able to demonstrate compliance with GDP requirements.

Implementation
Each activity performed by the RP should be included in a procedure which forms part of the Quality Management System. The procedures should define what activity is required, when it is required, who is responsible, how it should be carried out and what needs to be documented. Making use of controlled forms/templates linked to the procedure helps to ensure that the required information is provided in a consistent manner

The responsibilities of the responsible person include:

Implementation
(i) Ensuring that a QMS is implemented and maintained
To do this, the RP should always be sufficiently involved with the QMS to ensure ongoing compliance with GDP, especially with respect to proposed changes. Where the RP cannot attend management review meetings, he/she should ensure that they receive output of the meeting for review and approval.

(ii) Focussing on the management of authorised activities and the accuracy and quality of records
The RP should ensure he/she is aware of the details of the Wholesale Dealer Authorisation (WDA) and the systems and documentation supporting them. The RP should develop a procedure to what records should be checked for accuracy and quality. Some authorities may permit some of these checks to be delegated to appropriately trained personnel; however, the accountability of the accuracy of the records will remain with the RP.

(iii) Ensuring that initial and continuous training programmes are implemented and maintained
The RP would typically be involved in establishing and approving the training programme for the company. The RP should encourage the company to develop a training matrix where the training requirements for each role can be assigned. The RP may also choose to conduct some training sessions as it is a good way to receive feedback on various aspects of the QMS. Training records should be reviewed in self-inspections and the RP made aware if there are any gaps/delays to training plans.

(iv) Coordinating and promptly performing any recall operations for medicinal products
The RP plays a pivotal role in any recall operation and provides a key communication and coordination link between the company, regulatory authorities and suppliers/customers. The company recall procedure should detail the process and the responsibilities of the RP.

(v) Ensuring that relevant customer complaints are dealt with effectively
In small organisations, the RP may personally deal with all quality related complaints. In larger organisations, the RP should be made aware at minimum and ideally be involved in all significant quality complaints, plus any that may relate to falsified product. The RP should also collate and review the trend of complaints periodically to ensure he/she is aware of the level and frequency of complaints. The RP should develop Technical Agreements with each marketing authorisation holder which defines types of complaints which require referral including the reporting timescales. It is particularly important that any medical complaints, adverse reactions and concerns are referred to the appropriate Marketing Authorisation Holder's medical team promptly.

(vi) Ensuring that suppliers and customers are approved
The RP should develop a procedure defining the process for checking bona fides of the suppliers and customers with reference to nationally available information. Regulatory approval for both suppliers and customers can change and the RP should have a system for understanding how this information can be obtained nationally to enable their database to be updated. Ensuring these activities are included in regular internal audits should provide ongoing assurance that the system is working.

(vii) Approving any subcontracted activities which may impact on GDP
The RP should be involved in the selection, audit and approval of any subcontracted activities and will be a signatory on the corresponding Technical/Quality Agreement.

(viii) Ensuring that self-inspections are performed at appropriate, regular intervals following a prearranged programme and necessary corrective measures are put in place
The RP should prepare an annual self-inspection programme for the company. The RP may personally get involved in a number of self-inspections, e.g. covering high risk areas and/or those with a poor compliance record. It is highly recommended that the RP has been trained in auditing.

(ix) Keeping appropriate records of any delegated duties
Routine delegated tasks should be defined in appropriate procedures. Where a task has been delegated which is not defined in a procedure, then this delegation should be formally recorded. Records should include, in sufficient detail; what, who, when and for how long, so that no misunderstandings occur.

(x) Deciding on the final disposition of returned, rejected, recalled or falsified products
The RP should develop a procedure defining the criteria for final disposition of returned, rejected, recalled or falsified products. This is a key role for the RP and all decisions taken should be justified and documented.

(xi) Approving any returns to stock
The criteria for acceptance of the returns back to stock should be defined in a procedure based on the either the details in the technical agreement with the Marketing Authorisation Holder (MAH) or with reference to regulatory guidelines. These standards may include assessment of any potential tampering, and the transportation conditions including temperature data. Where checks undertaken have indicated that certain returns can be approved for return to stock; the RP needs to review each situation in detail, assure him/herself that it is acceptable to do this and personally approve this transaction.

(xii) Ensuring that any additional requirements imposed on certain products by national law are adhered to[2]

2 Article 83 of Directive 2001/83/EC

It is a key part of the RP role to ensure they keep up to date with requirements for certain types of products e.g. Controlled Drugs. The RP should ensure he/she has easy access to web sites or other sources of information that provide alerts to any proposed changes to legislation that could affect any product in one of these categories.

2.3. Other personnel

There should be an adequate number of competent personnel involved in all stages of the wholesale distribution activities of medicinal products. The number of personnel required will depend on the volume and scope of activities.

What is the rationale for this point of guidance?
Work volumes need to be balanced with the number of personnel to ensure execution of work activities is carried out as planned and in a controlled manner. Any imbalance can stress normal operations, creating the risk of errors that can adversely impact the patient.

What are the benefits and risks associated with this point of guidance?

Benefits
- An adequate balance between the activities to be performed and the personnel to perform them will ensure a correct flow of the business. This will be beneficial in providing assurance of the quality of the product and reducing risk but also provide a high level of customer satisfaction by having an optimized service;
- A good alignment / coordination between resources and workload allows time for other activities (e.g. training when the volume of work is low).

Risks
There are number of risks which may result from an imbalance between workload and personnel, e.g.:
- Personnel may take short cuts in procedures with increased probability of errors;
- Training plans may be compromised;
- Internal audit programmes may be delayed or cancelled;
- Absenteeism and staff turnover may increase which would exacerbate the problem.

Implementation
It is the responsibility of senior management and the RP, to jointly ensure a proper balance between resources and workload. Examples of how this may be achieved are:
- Having ongoing dialogue with the staff regarding concerns and responding appropriately;
- Anticipate peaks in workload (e.g. seasonal activities) and manage coverage for holiday periods and hire staff to enable training to occur in good time.

Note: Lean – Six SIGMA tools or similar processes can be used to help to align resources to the workload (i.e. pull methods, Kanban systems.)

The organisational structure of the wholesale distributor should be set out in an organisation chart. The role, responsibilities, and interrelationships of all personnel should be clearly indicated.

What is the rationale for this point of guidance?
- Defined responsibilities ensure processes are executed in a controlled manner and that there are no gaps created due to lack of clarity;
- Communication channels required or both routine activities and non-routine situations are clarified.

What are the benefits and risks associated with this point of guidance?

Benefits
An organisation where the responsibilities, functions and interrelationships are clearly defined
- Reduces risk of non-compliance due to lack of clarity of roles;
- Minimises the chance of gaps in responsibilities occurring.

Risks
Where roles and responsibilities are not defined, then the following risks exist:
- Activities can be duplicated – waste of resources;
- Some activities may not be performed due to assumption that somebody else is responsible;
- In emergency situations or in cases of deviations, the organisation may not be capable of reacting appropriately due to lack of clear responsibilities.

Implementation
Examples of how this might be implemented are:
- By mapping the processes and identifying the stakeholders for each operation, information and document flow;
- Ensuring responsibilities, controls and actions to be taken are included in job descriptions, procedures or RACI (Responsible-Accountable-Consulted-Informed) charts;
- Managers communicating responsibilities clearly during the induction training and clarifying any KPIs/Quality indicators for which the person is responsible.

The role and responsibilities of employees working in key positions should be set out in written job descriptions, along with any arrangements for deputising.

What is the rationale for this point of guidance?
Written job description ensures individuals are clear on their role and responsibilities within the organisation and there is no ambiguity.

What are the benefits and risks associated with this point of guidance?

Benefits
- Personnel have a clear understanding of their role and the organisation's expectations of them;
- Helps management to build a robust organisation and achieve a controlled, standardised operation;
- Assists Human Resources in attracting talent and developing personnel.

Risks
See previous section regarding risks where roles and responsibilities are not defined.

Implementation
- The manager defines the responsibilities in conjunction with the Human Resources (Personnel) Department normally sets the organisational framework for the document;
- Job descriptions should be subject to continual review to ensure they reflect the current expectations.

2.4. Training

All personnel involved in wholesale distribution activities should be trained on the requirements of GDP. They should have the appropriate competence and experience prior to commencing their tasks.

What is the rationale for this point of guidance?
Pharmaceutical wholesalers handle medicines which may have specific storage, security, and handling requirements. EU GDP describes specific requirements for storage, handling and transportation of medicines, it is therefore important for the individuals performing tasks in the company have a good understanding of these requirements to avoid errors and misunderstanding.

What are the benefits and risks associated with this point of guidance?

Benefits
Trained personnel who have good understanding of the processes, procedures and product requirements will operate within the company's QMS framework ensuring medicines safety, integrity and security during storage and transportation. Trained personnel will be able to understand and see problems when they occur, follow the proper reporting procedures, inform the management so that appropriate action can be taken. Providing adequate training to staff enables them to perform effectively minimising any risks to the products they are handling.

Risks
Lack of training could result in:
- Damage to the products;
- Security of the medicines being compromised, e.g. falsified medicines entering the market;
- Important medical queries/safety information (pharmacovigilance (PV) data) not being communicated;
- Significant commercial losses, e.g. recalls;
- Failure of all or part of the QMS, putting pressure on other areas (and individuals) through poor decision making;
- Suspension of the company's licence (WDA).

Note: there is a particular risk associated with recruitment of temporary personnel who may be employed at very short notice with low levels of understanding of GDP, and the risks associated with the activities which will probably be new to them.

Implementation

- Senior management and RP to develop the company training programme and standards;
- All staff (including temporary staff) to receive initial training in GDP upon joining the company;
- Training program to include provisions for continued review and update of training, including annual GDP refresher training;
- RP to provide direct input into the design and implementation of a GDP induction and an ongoing refresher programme for all personnel;
- GDP training to be made relevant to the different roles;
- Develop a mechanism to ensure that persons not yet trained in GDP are not allowed or asked to complete any relevant tasks. This can be achieved by good management oversight of the training programme and matrix for their direct reports. It also relies on personal integrity of individuals to resist the temptation to complete tasks for which they have not been inducted or trained and the training programme should emphasise this.

The national regulatory requirements for training RPs vary. As a minimum, good understanding of the GDP requirements is expected. As this is a developing scenario you should check on the current national regulatory expectations. E.g., in UK, a COGENT Gold Standard was developed by the industry supported by the MHRA. See also the ECA code of practice for RPs.

Personnel should receive initial and continuing training relevant to their role, based on written procedures and in accordance with a written training programme. The responsible person should maintain their competence in GDP through regular training

What is the rationale for this point of guidance?
For a QMS to remain effective; training should be comprehensive and updated regularly to ensure GDP standards and regulatory requirements are continuously met.

What are the benefits and risks associated with this point of guidance?

Benefits
A well-designed induction programme and on-going training helps ensure personnel are equipped with the correct knowledge to carry out their duties effectively and efficiently. This minimises the number of non-conformances or deviations that occur due to poor or incomplete training.

A RP who successfully maintains their knowledge of GDP and regulatory requirements is able to act as figurehead in driving the compliance of the organisation and can act as a key trainer of other personnel. This in turn helps drive continuous improvement of quality standards and procedures within the QMS.

Risks
See previous section regarding risks associated with a lack of training.

Implementation
The overall training programme is often captured in a training matrix. This method is effective and can be tailored to roles and departments. Training frequency and results of competency tests can also be captured along with prompts for retraining. A simple spreadsheet can be effective providing it is regularly maintained and reviewed. Training should be clearly split into stages linked with activities that may subsequently performed by the individual.

Training processes can be split into 4 stages:

1. Training needs identification
2. Training guides developed (SOPs)
3. Training implementation
4. Training outcomes evaluation

These different stages are further elaborated below.

1. Training needs identification
This should be based on:

- Organisational Analysis – e.g., Objectives, Resources, Organisational climate and culture
- Job Analysis – i.e., job description and specification
- Individual Analysis – i.e., knowledge, skills and abilities

2. Training guides developed
The training plan provides the framework to describe details of the GDP requirements. These need to be described in SOPs. Key factors are:

- All personnel are trained to adequately perform the assigned job and responsibilities
- Training is performed according to approved SOP(s)
- Employees are continually trained in procedures relevant to their responsibilities

Factors to consider for the training schedule include:

- An annual training plan (incorporating GDP requirements) is prepared, then reviewed and approved by QA and the RP
- Time is allocated for training sessions – taking account of any shift working patterns.

3. Training programme implementation

i. **New employee training**
Includes general training, basic and intermediate GDP training, safety procedures, work methods "on the job training", and a qualification/ certification process.

ii. **Existing employee training**
Includes annual GDP continuing education training, new SOP training, re-training on revised SOPs and professional development training.
Note: the requirement for annual refresher GDP training may be more effectively achieved by having several short discussion sessions on recent quality incidents and the corrective actions taken. This should be supplemented by specific training on any GDP requirements.

iii. **Corrective training**
In the case of human error or a deviation from an existing procedure, the relevant department head and/or QA will define the corrective training requirements.

iv. **Management continuing education training**
Department heads and team supervisors will take part in management training sessions throughout the year, to enhance their management skills and techniques. These training sessions could be performed as a group or on a 1:1 basis with a personal coach.

4. Training Outcomes Evaluation

It is an expectation that all training be assessed for effectiveness where the person is expected to remember the specific requirements. Where possible, in a practical situation, a new skill acquired can be demonstrated by the trainee to show that they understand how to perform the task. This should be demonstrated on more than one occasion to provide greater assurance. Where the training is designed to transfer important knowledge, course assessments should be included with a clear pass/fail mark and an established process to follow for those who are unsuccessful. This may be achieved using a short questionnaire or a multiple choice quiz.

The RP can maintain their understanding of the current requirements by:

- External site visits
- Attending regulatory and industry symposia and conferences
- Building a network of RP colleagues
- Referring to national regulatory websites for current updates

In addition, training should include aspects of product identification and avoidance of falsified medicines entering the supply chain.

What is the rationale for this point of guidance?

In an industry increasingly at risk of falsified product entering the legitimate supply chain and posing a risk to patient safety, it is important for staff handling the products to be able to identify falsified medicines they may receive. Training in identifying falsified medicines can help staff to identify the potential risks and report any suspicious medicines to the management.

What are the benefits and risks associated with this point of guidance?

Benefits

Trained staff help protect the patients with early identification of potential falsified medicines they handle. The organisation also benefits from reduced impact on supplies and costs of recalls. The industry as a whole benefits from any falsified product being seized where the sources of introduction can be identified and those responsible prosecuted.

Risks

Products which enter the distribution chain under the guise of reputable brands may not be identified and quickly find themselves in the hands of the patient with a potential risk to their health. The further a falsified product goes through the distribution chain, the more complex and difficult any recall of the product will be.

Implementation

A written procedure for checking the in-coming products to include specific checks relating to unique identifiers, sites of manufacture and distribution in accordance with the documented supply chain.

Personnel to receive training in understanding the complexities of supply chains with emphasis on how these may be exploited by counterfeiters. This should be re-enforced by examples of falsified product and how they may be distinguished from genuine product.

Good communication and working relationships with the Marketing Authorisation Holder should be established, for example ensuring any changes to product identifiers, sites of manufacture and issuance of Certificates of Analysis are informed to the distributor. This should be captured in the Quality/ Technical Agreement between the relevant parties. Particular attention should be paid to partly opened packs, damaged pallets and opened boxes as possible indicators of falsified products.

Personnel dealing with any products which require more stringent handling conditions should receive specific training. Examples of such products include hazardous products, radioactive materials, products presenting special risks of abuse (including narcotic and psychotropic substances), and temperature-sensitive products.

What is the rationale for this point of guidance?
Hazardous products represent risks both to staff working at the distributor and all other personnel subsequently handling them in the supply chain. This places a particular emphasis and responsibility on the need to protect them at all times.

What are the benefits and risks associated with this point of guidance?

Benefits
Personnel specifically trained in these requirements will reduce the risk of non-conformances and any occupational health issues for both themselves and other personnel within the supply chain.

Risks
If handled incorrectly there is a risk to product quality and to personnel involved in the handling such materials. This may be of particular concern when disposing of medicinal product.

Implementation
- Use published guidance on cold chain or any other specialised products;
- Ensure precautions in hazard data sheets are incorporated into procedures;
- Obtain information from the manufacturers about sensitivity of the products to heat, light, humidity etc. Note: this should be in the technical agreement.

A record of all training should be kept, and the effectiveness of training should be periodically assessed and documented.

What is the rationale for this point of guidance?
Complete training records enable management to track training needs of individuals and the company as a whole and therefore address any knowledge or experience gaps as required. Some procedures are critical to product quality; therefore, effectiveness of training on these is of paramount importance, e.g. checking data records for cold chain products. In the absence of training assessment, it is difficult to know if the trainee has understood the procedural requirements and can perform the task competently. Documentation of this assessment allows for weaknesses in the training programme to be identified and corrected in a timely manner.

What are the benefits and risks associated with this point of guidance?

Benefits
Well documented training facilitates root cause investigations and the review of the effectiveness of training where any gaps in the overall training programme can be identified and addressed to strengthen processes and GDP compliance. Records of training provide assurance to the regulators and customers during their audits staff have been trained adequately.

Risks
Risks associated with an absence of appropriate training documentation include:
- Management is unable to monitor the effectiveness of training;
- Inability to demonstrate to regulatory agencies/customer auditors adequate training has been provided to staff;
- Inability to plan future training based on experience/competency.

Implementation
The procedure for training should detail how the records should be kept and how and when assessment should be carried out.

Training records normally include:
- A title of the topic and a reference to the material used. E.g., SOP No. with version number;
- The trainee's name;
- The trainer's name;
- Date;
- Trainee's signature showing they have understood the training provided;
- Sign off/completion statement from the trainer.

Note: Many companies include this information in their matrix records to help management and some display it publicly. Training records for each individual along with results of any assessments should be kept in their personal training folder.

This should be accompanied by an overview of the training requirements for their role within the organisation. Where training is performed by external providers, details of the trainer's credentials and experience should be kept on file along with the training material used.
Different assessment methods are possible e.g.
- Check knowledge with a test;
- Observe competence in practice;
- State when the person is a trained Trainer.

The organisation needs to decide and record what level of assessment is required for different procedures/activities. For example, training in GDP will probably require a knowledge test whereas training in use of data loggers will probably require assessment of practical competence.

The RP should be involved or have sight of the output of training assessments and data should be trended and used to benchmark standards.

Periodic assessment of training ensures that standards are maintained and that the manner of delivery remains appropriate.

2.5. Hygiene

Appropriate procedure relating to personnel hygiene, relevant to the activities being carried out, should be established and observed. Such procedures should cover health, hygiene and clothing.

What is the rationale for this point of guidance?

In any organisation, good health is essential for individuals to perform their tasks efficiently, correctly and to a good standard. In order to ensure this, an organisation has to ensure these standards are defined. To assist people involved, fulfil their tasks correctly, clothing/uniforms may need to be provided. There will need to be a process in place to manage the cleaning and maintenance of this work wear.

What are the benefits and risks associated with this point of guidance?

Benefits

Management of staff health hygiene will reduce risk of product contamination and transmitting health issues amongst staff.

Risks

Health

- Poor health of individuals may result in poor performance of their given tasks. This may lead to errors which will ultimately result in increased workload.
- The potential of affecting other staff may result in insufficient personnel i.e. literally not enough people to perform all the tasks required. The organisation may try to continue using staff who do not fully understand what the role is, or may not have been trained on how to perform tasks correctly and what to do if something goes wrong.

Hygiene

- The risk of poor hygiene is much the same as above. It will in addition lower staff morale, result in contaminated products and poor work practices.

Clothing

- Poor clothing is a risk particularly in areas where a lot of physical activity is involved. The biggest risk is to the organisation where an injury to an individual may result, which will cost the organisation financially as well as affecting work efficiency.

Implementation

Each organisation / site should ensure appropriate procedures to describe measures in place and procedures to follow to maintain good hygiene practices and avoid heath risk to staff.

Locate washrooms in appropriate areas to ensure that hands are washed after using toilets. Canteens or designated eating areas with lockers for food storage and drinks machines etc. should be provided so that no food, drinks etc. are brought into the work areas. Chewing, drinking, or eating should not be allowed in any areas other than these dedicated areas. Also, no personal medication is allowed in the operational areas. Likewise, a designated smoking area should be provided.

Health and Safety person(s) should be appointed on site to ensure these aspects of the organisation are compliant.

Special attention should be paid to the following points when considering health and hygiene issues:

Health

Good health will ensure that individuals are fully focused on their activity. They are also able to conduct the work efficiently especially in areas which may involve a lot of physical activity.

Personnel not in good health, especially those suffering conditions which could be passed onto other staff, e.g., flu, diarrhoea, should be discouraged from attending work to avoid affecting other colleagues. This is a vital consideration where a pandemic e.g. bird flu etc. is involved.

Hygiene

In addition to providing washrooms, canteen/designated eating areas, and storage for personnel items, rules relating to cleaning of any provided work wear are essential to maintain a good standard of clothing. Good presentation of individuals is important as it identifies them as employees and makes them feel good about themselves as well as to any outside visitors. This is particularly important where individuals are involved in delivering to patient homes.

Clothing

Protection of individuals especially in areas such as picking, packing, and transportation of medicinal products is important. This will not only assist individuals, who will be able to work comfortably in the correct work wear and be protected e.g. hard hats for head protection from products stored at high levels; safety shoes etc., but also protect products from potential damage as

staff are able to work without concerns of their safety, thus taking time and care with products they are handling.

Suitable clothing/work wear will vary with the tasks being performed by individuals. Some suggestions are as follows:

- **Pick/Packing operators:** Strong pair of closed shoes with hard toecap, and good protective coveralls with no pockets. If working in cold pack areas then suitable gloves and fleeces/coats should also be included.
- **Forklift operator:** Same as pick/pack operator, but should have a hard hat as well if the storage areas have high racking.
- **Drivers:** Smart trousers and jackets preferably with company logo. However, drivers delivering to homecare patients may need more discreet clothing.

Chapter 3 – Premises and Equipment

3.1. Principle

Wholesale distributors must have suitable and adequate premises, installations and equipment[1], so as to ensure proper storage and distribution of medicinal products. In particular, the premises should be clean, dry and maintained within acceptable temperature limits.

(1) Article 79(a) of Directive 2001/83/EC

What is the rationale for this point of guidance?

Medicinal products often require specific storage conditions to maintain their quality during their shelf life. In addition there is a risk of product contamination through adverse weather or pest ingress, therefore wholesalers are required to have and to maintain adequate facilities for storage and transportation of medicinal products. Companies need to determine what is 'proper', 'adequate' or 'suitable' for the activities they undertake.

What are the benefits and risks associated with this point of guidance?

Benefits

Well designed and maintained facilities, in compliance with GDP, minimise the risk of product spoilage, damage or contamination, which in turn, safeguards patients.

Risks

- Inadvertent distribution of non-approved product, due to poor segregation and control;
- Product contamination, from external events, e.g. rain and flooding;
- Product degradation due to temperature fluctuations, light or humidity;
- Ingress of pests causing damage to products;
- Physical damage to product.

Implementation

- Use the detail in each section of this guidance as a basis for a gap analysis;
- If gaps are identified, potential risks to the organisation can be used to influence colleagues and management to support appropriate corrective or preventive actions (CAPA).

3.2 Premises – Editors notes

This section is large and covers a number of different aspects so, for clarity, it has been broken down into different sub-sections for treatment in this guidance document.

The Commission Guideline does not sub-number the paragraphs in this section, but, for ease of reference, these have been added to this document using square brackets together with an indication of aspects covered.

Rationale and Risk/Benefits sections have been omitted from the guidance on these points, keeping the focus on understanding and implementation, with reference to other information where appropriate. For general coverage of the Rationale and Risks/Benefits for this Chapter, see 3.1.

3.2. Premises ((i) Facility design)

The premises should be designed or adapted to ensure that the required storage conditions are maintained. They should be suitably secure, structurally sound and of sufficient capacity to allow safe storage and handling of the medicinal products. Storage areas should be provided with adequate lighting to enable all operations to be carried out accurately and safely

Implementation

- A user requirement specification (URS) should be drawn up to provide clarity regarding the intended use of any facility. Factors for consideration are;
  - Capacity required (number of pallet spaces at maximum load) for different types of storage e.g. frozen, refrigerated, controlled ambient, quarantined, approved, returned and rejected;
  - Functional requirements for security, e.g. doors, cameras, alarms;
  - Construction material specifications to facilitate cleaning and minimise physical damage during use;
  - Arrangement for flow of material and personnel e.g. through segregated receipt and dispatch areas to minimise the risk of mix-ups;
  - Any particular requirements for the different areas, e.g., temperature control at 2-8°C for a 'pick and pack' area for cold chain products;
- For a new build facility, the URS should drive the detailed design and qualification process;
- For existing facilities, conduct a gap analysis against the URS and create an action plan to address any gaps found;
- A facility which is "structurally sound" will be expected to be resistant to pests (birds, insects, rodents) and weather, and should include impervious flooring and well-sealed doors. See section 3.2(vii) for more detail on pest control measures;
- Localised lighting will be expected to be sufficient for reading labels, etc. without being so strong as to cause light damage to products or their packaging. Direct sunlight or artificial light sources that generate significant heat should be avoided;
- Ensure that an appropriate maintenance programme is put in place to prevent any deterioration in standards (general building fabric, finishes, equipment or utilities) and that this is supported by the change control process;
- Self-inspections inform management of the improvements required;
- Guides produced by ISPE (for example) might be helpful for more detail on facility design matters.

3.2. Premises ((ii) Contract premises)

Where premises are not directly operated by the wholesale distributor, a contract should be in place. The contracted premises should be covered by a separate wholesale distribution authorisation.

Implementation

- Formal processes should be in place for outsourcing activities, including the assessment of their suitability and contractual arrangements (ensuring that an agreed contract is in place before any usage).
- For further details, see the relevant sections elsewhere in the EU GDP Guideline – Section 1.3 'Management of outsourced activities' and Chapter 7 'Outsourced Activities'

3.2. Premises ((iii) Segregation of different materials)

Medicinal products should be stored in segregated areas which are clearly marked and have access restricted to authorised personnel. Any system replacing physical segregation, such as electronic segregation based on a computerised system, should provide equivalent security and should be validated.

Products pending a decision as to their disposition or products that have been removed from saleable stock should be segregated either physically or through an equivalent electronic system. This includes, for example, any product suspected of falsification and returned products. Medicinal products received from a third country but not intended for the Union market should also be physically segregated. Any falsified medicinal products, expired products, recalled products and rejected products found in the supply chain should be immediately physically segregated and stored in a dedicated area away from all other medicinal products. The appropriate degree of security should be applied in these areas to ensure that such items remain separate from saleable stock. These areas should be clearly identified.

Special attention should be paid to the storage of products with specific handling instructions as specified in national law. Special storage conditions

(and special authorisations) may be required for such products (e.g. narcotics and psychotropic substances).

Radioactive materials and other hazardous products, as well as products presenting special safety risks of fire or explosion (e.g. medicinal gases, combustibles, flammable liquids and solids), should be stored in one or more dedicated areas subject to local legislation and appropriate safety and security measures.

Implementation

- Arrangements for the segregation of the different materials mentioned should be defined in procedures;
- Generally, computerised (electronic) segregation is accepted, where validated, but certain scenarios are specified as requiring physical segregation. Some regulatory authorities have differing perspectives on this point, so it is important to understand specific national requirements;
- Where physical segregation is specified, these areas should be managed such that access is restricted to authorised personnel only;
- Personnel with access to electronic systems should have unique user identifications and passwords to allow clear traceability of actions taken;
- Staff access within electronic systems should be linked to the functionality that is required for completion of specified tasks within a procedure upon which they have been trained. The ability to change material status should be limited to the Responsible Person or designate;
- An IT policy should be in place for the management of system access and passwords in line with EU GMP Annex 11, Section 12;
- There should be a suitable system and associated procedures in place, to ensure that all products are reviewed and assessed on an ongoing basis against any changes to specific handling instructions, specified under relevant national legislation;
- Stock reconciliation should be carried out at regular intervals;
- Storage areas for controlled substances should be segregated and physically secure in accordance with national legislation;
- Relevant experts should be consulted to ensure adequate storage areas, safety controls and staff training are in place for any radioactive materials handled;
- For more on computerised systems, see Section 3.3.1, EU GMP Annex 11 and GAMP5;
- The Bibliography includes examples of national requirements for handling specific products (UK controlled drugs legislation and guidance).

3.2. Premises ((iv) Receiving and Dispatch areas)

Receiving and dispatch bays should protect products from prevailing weather conditions. There should be adequate separation between the receipt and dispatch and storage areas. Procedures should be in place to maintain control of inbound/ outbound goods. Reception areas where deliveries are examined following receipt should be designated and suitably equipped.

Implementation

- Protection from adverse environmental conditions can be achieved via a combination of an external canopy, vehicle tunnels, appropriate doors and procedures during receipt and dispatch;
- Adequate separation between receipt and despatch areas can be achieved with logical product flow reflected by clear signage and floor markings to identify inbound/outbound areas;
- Ensure that adequate space and lighting is available for all of the activities required in receipt/despatch procedures.

3.2. Premises ((v) Security)

Unauthorised access to all areas of the authorised premises should be prevented. Prevention measures would usually include a monitored intruder alarm system and appropriate access control. Visitors should be accompanied.

Implementation

- Based on risk assessment, create a procedure on access control for staff and visitors and ensure all staff are trained to follow it;
- Install alarm and camera systems covering perimeters and access points to provide 24 hour/7 days per week monitoring and enable any access issues to be highlighted and acted upon immediately;
- Where permitted by national legislation, a risk-based approach should be taken to staff security checks prior to employment.

3.2. Premises ((vi) Cleaning)

Premises and storage facilities should be clean and free from litter and dust. Cleaning programmes, instructions and records should be in place. Appropriate cleaning equipment and cleaning agents should be chosen and used so as not to present a source of contamination.

Implementation

- Maintain the cleanliness of any premises used to receive, store or dispatch products so as to safeguard their quality;
- Dust, dirt and /or the ingress of mould or fungal spores can contaminate products or packaging rendering them unsuitable for distribution;
- The cleaning regime should be systematic and should cover all areas, including racking, at a frequency sufficient to maintain cleanliness;
- Cleaning procedures should cover the handling of spillages;
- All cleaning should be recorded. Checklists may be useful;
- Periodic checks for fungal/mould growth should be made, especially in cold stores;

- The effectiveness of cleaning should be assessed as part of the self-inspection programme;
- Cleaning equipment such as mops should be kept clean and dry and periodically replaced so as not to present a source of contamination;
- Cleaning agents need careful selection to ensure that products are not damaged by chemical reaction or tainted by odour. Disinfectants and cleaning agents should be specified in procedures and the use of alternatives prohibited.

3.2. Premises ((vii) Pest control)

Premises should be designed and equipped so as to afford protection against the entry of insects, rodents or other animals. A preventive pest control programme should be in place.

Implementation

- Typically, licensed pest-control experts are sub-contracted to provide advice and a pest control service. A contract should be in place to cover such work, together with a procedure or statement of work;
- A risk assessment of entry points for different types of pest should be performed annually or after major changes to identify potential risk areas;
- Appropriate arrangements to address these risks should then be developed, possible solution might include:
  - Insect killing devices;
  - Rodent bait traps;
  - Avoiding any opening windows where possible; using mesh over any opening windows that exist;
  - Air blankets or curtains at large entry points to prevent access by birds;
- Pest control agents should be selected and their use controlled to avoid the risk of contaminating products:
  - Agents used should be documented in a procedure or the contract with the licensed pest control company and should be 'food safe'. No other agents should be permitted on site;
  - The spraying of chemicals should not to be permitted within the warehouse;
  - Certificates relating to pest control agents and records of their use should be retained; these may be asked for by regulatory inspectors;
- The location of all the above measures should be included on the site plan;
- Regular checks on pest activities should be performed to ensure their effectiveness. The frequency of these checks should be specified and results documented;
- Trained personnel should regularly review records and reports to flag any required corrective actions to management;

3.2. Premises ((viii) Staff facilities)

Rest, wash and refreshment rooms for employees should be adequately separated from the storage areas. The presence of food, drink, smoking material or medicinal products for personal use should be prohibited in the storage areas.

Implementation

- Policies must be documented and communicated;
- Eating, smoking and drinking should be permitted only in segregated areas away from product handling and storage areas and designated for this purpose;
- Management should provide appropriate facilities (e.g. personal storage space, such as lockers), services (provision and laundry of work clothing) and instructions to personnel to enable compliance with these requirements.

3.2.1. Temperature and environment control

Suitable equipment and procedures should be in place to check the environment where medicinal products are stored. Environmental factors to be considered include temperature, light, humidity and cleanliness of the premises.

An initial temperature mapping exercise should be carried out on the storage area before use, under representative conditions. Temperature monitoring equipment should be located according to the results of the mapping exercise, ensuring that monitoring devices are positioned in the areas that experience the extremes of fluctuations. The mapping exercise should be repeated according to the results of a risk assessment exercise or whenever significant modifications are made to the facility or the temperature controlling equipment. For small premises of a few square meters which are at room temperature, an assessment of potential risks (e.g. heaters) should be conducted and temperature monitors placed accordingly.

Implementation

- Conduct an initial risk assessment to document the environmental requirements for all the products which are to be stored, based on the relevant manufacturer's packaging and labelling;
- Warehouse temperature monitoring should be based on a mapping exercise to identify the positions where temperature control is poorest. Wherever possible, the first mapping exercise should be carried out before the area is used to show that suitable conditions have been met before products are introduced;
- 'Representative conditions' can be fairly simple to simulate in the case of smaller environments such as cold stores and fridges/freezers, where it should be possible to challenge the environment with a dummy load.

This will then allow the environment to be mapped and challenged (with impact tests) without compromising product quality. In the case of a large warehouse, it would not be practical to use dummy loads and may be best achieved by mapping again once the facility is fully operational with product in place;

- Once the initial exercise has been completed, the data should be assessed and used to determine where the most suitable locations are for the placement of Continuous Monitoring Probes (CMPs). These are typically locations seen to have experienced the largest temperature fluctuations;
- Repeat exercises should then be carried out based upon the results of a risk assessment. Points for consideration in the assessment can include:
  - the status and results of mapping work already carried out;
  - any known deviations (alarms) outside of the set parameters and any corrective actions;
  - summary of continuous monitoring data;
  - any changes made to the last mapping as well as any planned change that could affect airflow or temperature;
  - any maintenance activities carried out or planned for the future;
- The ongoing suitability of the number of CMPs in place and their locations should be assessed following each mapping exercise;
- The risk assessment should be reviewed on a regular basis. The mapping of cold stores, fridges and freezers is often repeated annually although this should still be part of the risk assessment and justification should be provided for the chosen interval;
- A risk-based approach, supported by historical data, should be taken to determine whether seasonal variations need to be subject to repeated mapping exercises to cover the range of ambient (external) temperatures;
- Reviews of monitoring and control practices should be conducted periodically, as part of a self-inspection programme and mapping repeated if required.

See Bibliography for possible sources of further information relating to risk assessment, environmental monitoring and validation. With thanks to Kane Edgeworth of Biomap, example temperature mapping protocol and report templates are available from the ECA and PQG websites.

3.3 Equipment

All equipment impacting on storage and distribution of medicinal products should be designed, located and maintained to a standard which suits its intended purpose. Planned maintenance should be in place for key equipment vital to the functionality of the operation.

Equipment used to control or to monitor the environment where the medicinal products are stored should be calibrated at defined intervals based on a risk and reliability assessment.

Calibration of equipment should be traceable to a national or international measurement standard. Appropriate alarm systems should be in place to provide alerts when there are excursions from pre-defined storage conditions. Alarm levels should be appropriately set and alarms should be regularly tested to ensure adequate functionality.
Equipment repair, maintenance and calibration operations should be carried out in such a way that the integrity of the medicinal products is not compromised.

Adequate records of repair, maintenance and calibration activities for key equipment should be made and the results should be retained. Key equipment would include for example cold stores, monitored intruder alarm and access control systems, refrigerators, thermo hygrometers, or other temperature and humidity recording devices, air handling units and any equipment used in conjunction with the onward supply chain.

Implementation

- The organization should identify all equipment that impacts upon product quality. e.g. HVAC systems, alarms, measuring equipment and, for those facilities performing labelling operations, printers, barcode scanners, etc;
- The equipment list should define the requirements for maintaining and calibrating each separate item, at serial number level. Software packages for managing equipment maintenance are frequently used to achieve this;
- The (preventive) maintenance required and its frequency should be defined for each piece equipment/ type of equipment based on risk assessment. Guidance on preventive maintenance requirements can typically be obtained from the equipment manufacturer;
- Completion of preventive and corrective maintenance should be documented (maintenance certificates). These records should make reference to the equipment (individual identification) and the maintenance activities carried out;
- For equipment deemed critical to operational continuity (e.g., temperature controls), consider the need for:
  - Alarms;
  - Critical Spares;
  - Service agreements, including emergency/out of hours cover;
- Risk and reliability assessments should be used to justify the intervals between calibrations;
- Calibration should preferably be 'multi point' to demonstrate accuracy

across the expected operating range of the monitored environment. Consideration should be given to extending the range to cover potential failures or events that will generate unforeseen temperatures. For example, a fridge sensor might be calibrated at -5/+5/+15°C, in order to cover potential failures resulting in decrease or increase of temperature;
- Knowledge of the tolerances of each measuring device should be used to guide the setting of alarms;
- A procedure should define the routes of communication and actions to be taken in case of alarm;
- To improve reliability and speed of response, consideration should be given to using automated systems to send alarm messages to personnel through SMS or mobile calls, etc;
- Calibration and tests of alarms should be included in the maintenance plan;
- All systems and records should be subject to regular self-inspection.

3.3.1 Computerised systems

Before a computerised system is brought into use, it should be demonstrated, through appropriate validation or verification studies, that the system is capable of achieving the desired results accurately, consistently and reproducibly.

A written, detailed description of the system should be available (including diagrams where appropriate). This should be kept up- to-date. The document should describe principles, objectives, security measures, system scope and main features, how the computerised system is used and the way it interacts with other systems.

Data should only be entered into the computerised system or amended by persons authorised to do so.
Data should be secured by physical or electronic means and protected against accidental or unauthorised modifications. Stored data should be checked periodically for accessibility. Data should be protected by backing up at regular intervals. Back up data should be retained for the period stated in national legislation but at least five years at a separate and secure location.

Procedures to be followed if the system fails or breaks down should be defined. This should include systems for the restoration of data.

What are the benefits and risks associated with this point of guidance?

Benefits
Adequate validation of a computerised system will demonstrate that the system meets the requirements defined for operations in the warehouse, and that risks associated with a potential failure of the system have been anticipated and either minimised or controlled.

Risks
Product data may be compromised if adequate validation is not carried out, if the description of the system is not accurate, if the system is not protected against unauthorised modifications, if it is not backed up or if there are no contingency plans in place in the event of system failures

- **Risks associated with the lack of validation:**
  The computer system (or partial applications of the computer system) cannot operate in an adequate manner. Examples of errors related to this are:
  - wrong expiry date recorded in the system;
  - a lot on hold can be released to a customer;
  - the lot number is not properly recorded in the system;
  - FEFO is not applied;
  - the system does not detect expired product;
- **Risks associated with inaccuracies in the description of the system:**
  Normally computer systems require customization to meet the requirements of a particular organisation. If the description of the system is incorrect uncontrolled changes create discrepancies. Valuable knowledge can be lost if it resides only with certain employees and is not written down;
- **Risks associated with lack of data protection:**
  If all personnel have access to the system set-up, the quality and/or traceability of the product is at risk;
- **Risks in not having procedures in case of system failure:**
  If the system fails and a contingency plan has not been defined, there is risk of shipping product which has not been subject to the controls that the system performs automatically (e.g. verification of FEFO, recording of information to ensure traceability etc.).

Implementation
- The approach to computerised system management, including validation, should be defined in a procedure;
- All computerised systems with the potential to impact product quality within the facility should be identified by risk assessment and documented;
- Using a risk-based approach and drawing from specialist guidance (see references), determine which systems require validation and which require verification of consistent operation;
- Steps in the validation process include:
  - URS (User Requirement Specification) to document what is expected

from the system;
  - DQ (Design Qualification);
  - IQ (Installation Qualification);
  - OQ (Operational Qualification);
  - PQ (Performance Qualification);
- Where appropriate documents might be combined for example IQ and OQ;
- It is recommended that the supplier of the computer system (or specialised IT department) supports the RP in defining the test protocols and acceptance criteria;
- A controlled document describing each system will help to ensure that all changes on the system are agreed with the organization and also will support the use of the system for example by new employees;
- Controls and access rights should be defined and implemented;
- All changes should be subject to a formal change control process;
- Regular backups of IT systems should be performed;
- A Business Continuity Management Plan and Disaster Recovery Plan should exist to cover the event of IT system failure;
- Further useful information can be found in EU GMP Annex 11, GAMP5 and ISO 9001.

3.3.2 Qualification and validation

Wholesale distributors should identify what key equipment qualification and/or key process validation is necessary to ensure correct installation and operation. The scope and extent of such qualification and/or validation activities (such as storage, pick and pack processes) should be determined using a documented risk assessment approach.

Equipment and processes should be respectively qualified and/or validated before commencing use and after any significant changes, e.g. repair or maintenance.
Validation and qualification reports should be prepared summarising the results obtained and commenting on any observed deviations. Deviations from established procedures should be documented and further actions decided to correct deviations and avoid their reoccurrence (corrective and preventive actions). The principles of CAPA should be applied where necessary. Evidence of satisfactory validation and acceptance of a process or piece of equipment should be produced and approved by appropriate personnel.

Implementation

- All processes and equipment with a potential to impact product quality within the facility should be identified by risk assessment and documented;
- For each process /equipment, protocols should be prepared which document the failure modes associated with each process/equipment. Verifications and/or inspections should be defined in the protocol, taking into account likelihood and potential impact of the failure and the probability of it being detected;
- Protocols should be executed and results documented. If the acceptance criteria defined within the protocol are met, the process/ equipment can be considered qualified. Otherwise, corrective / preventive actions should be implemented and documented;
- Protocols and associated reports should be approved by the Responsible Person or delegate within the quality organisation;
- Further useful information on Qualification and Validation may be found in EU GMP Annex 15.

Chapter 4 – Documentation

4.1. Principle

Good documentation constitutes an essential part of the quality system. Written documentation should prevent errors from spoken communication and permits the tracking of relevant operations during the distribution of medicinal products.

4.2 General

Documentation comprises all written procedures, instructions, contracts, records and data, in paper or in electronic form. Documentation should be readily available/retrievable.

With regard to the processing of personal data of employees, complainants or any other natural person, Directive 95/46/EC) on the protection of individuals applies to the processing of personal data and to the free movement of such data.

Documentation should be sufficiently comprehensive with respect to the scope of the wholesale distributor's activities and in a language understood by personnel. It should be written in clear, unambiguous language and be free from errors.

Procedure should be approved signed and dated by the responsible person. Documentation should be approved, signed and dated by appropriate authorised persons, as required. It should not be hand-written; although, where it is necessary, sufficient space should be provided for such entries.

Any alteration made in the documentation should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

Documents should be retained for the period stated in national legislation but at least five years. Personal data should be deleted or anonymised as soon as their storage is no longer than necessary for the purpose of distribution activities.

Each employee should have ready access to all necessary documentation for the tasks executed.

Attention should be paid to using valid and approved procedures. Documents should have unambiguous content; title, nature and purpose should be clearly stated. Documents should be reviewed regularly and kept up-to-date. Version control should be applied to procedures. After revision of a document, a system should exist to prevent inadvertent use of the superseded version. Superseded or obsolete procedures should be removed from workstations and archived.

Records must be kept either in the form of purchase/sales invoices, delivery slips, or on computer or any other form, for any transaction in medicinal products received, supplied or brokered.

Records must include at least the following information: date; name of the medicinal product; quantity received, supplied or brokered; name and address of the supplier, customer, broker or consignee, as appropriate; and batch number at least for medicinal product bearing the safety features[(2)].

Records should be made at the time each operation is undertaken.

(2) Article 80(e) and Article 82 of Directive 2001/83/EC

What is the rationale for this point of guidance?

Good quality documentation is the foundation of a quality system and provides the basis for detailed instructions and for the recording of information/ results. This helps to:

- Ensure that all staff work in a manner defined to ensure business efficiency and effective compliance with current good practices;
- Ensure that there is an audit trail and full traceability of all information relating to medicinal products;
- Demonstrate compliance with GDP;
- Form the basis of any investigation required when an issue arises.

Appropriate review and approval of documents should ensure clarity and freedom from errors, facilitating compliance with instructions and good record keeping which safeguards both patients and business.

Documents need to be readily available / retrievable

- For reference;
- To enable records to be made contemporaneously;
- To provide timely answers to questions/evidence during self-inspections, third party audits or regulatory agency inspections.

Failure to have instructional documents in place and readily available may result in staff undertaking activities without recourse to the instructions, thus increasing the risk of error.

Failure to have good recording systems in place and records readily available will result in an incomplete audit trail. At best, this will impact business efficiency, at worst it could compromise the integrity of the supply chain leading to risks to

patient safety and regulatory censure.

Complete records for each batch need to be available for at least the full duration of its life within the marketplace, hence the minimum retention period of five years (the maximum shelf life accepted by the European Medicines Agency for a marketed medicinal product). However, in many cases national legislation will take precedence and must be followed (a retention period of six or seven years is common).

Some of the data required to be held and processed as part of distribution activities, will fall within the scope of European Union legislation designed to protect individuals' right to privacy and there are penalties for infringements. It is therefore important that systems are in place for the compliant handling of such data and that staff are both aware of the applicable data protection legislation and trained in use of the company data handling systems.

The details in this section further set out the expectations and aid compliance.

Implementation
'Written documentation' covers both paper and electronic formats.

Documents fall into two main types:
1. Those which instruct and inform (e.g. Supplier Agreements; Technical Agreements; Policies; SOPs and work instructions). These are generally documents written by users and their managers.
2. Those which provide a record (e.g. check lists; reports; weight recordings; bar code readings, cleaning logs, etc.). These documents provide the "Audit Trail" evidence of activities, such as:
    a. What products were handled, when, where and by whom;
    b. The sources of the products;
    c. To whom those products were distributed;
    d. Under whose authorisation they were shipped;
    e. The bona fides of both suppliers and customers;
    f. Conditions of storage and transport;
    g. Investigations into any complaints or suspected falsified medicines;
    h. Actions taken in response to notifications of adverse reactions or recalls.

Overall documentation system requirements
Since the documentation system, comprising both instructions and records, is fundamental to the quality system, it needs to cover the full scope of operations.

Good documentation practice includes consideration of at least the following:

- Appointing a person (or department, depending on the size of the organization) to manage the documentation system;
- Deciding what documentation is required and the format (paper or electronic) in which it will be created, used and archived;
- Where electronic systems are used, these should be appropriately specified and validated to ensure data integrity – see EU GDP Guideline 3.3.1;
- Defining responsibilities for review and approval of each type of document;
- Ensuring all documents have clear purpose, unambiguous content and are kept up-to-date;
- Ensuring staff have ready access to the documents they need to refer to or complete as they perform their work;
- Training all staff to ensure that they understand the principles behind the required documentation practices – staff are more likely to be compliant with a requirement when they appreciate the reason for it;
- Recording data directly into official records (not on scraps of paper) at the time the operation is performed, which reduces the risk of errors arising from lapses of memory or transcription;
- For paper records, information should be recorded in pen with permanent ink, not using a pencil or some other means of recording that might not endure;
- For paper records, consideration of the way the document will be archived might drive requirements for use of particular ink colours and decisions regarding single or double-sided printing;
- Whenever records are made, care should be taken to ensure that they are legible, accurate and unambiguous so that they can be easily read and understood by someone else at a future date without recourse to the person who made them.

Define a record retention policy which takes into account all regulatory and business requirements and a procedure detailing how this will be achieved.

- In what format(s) will records be retained? e.g., original paper copies; electronic scans of paper documents; electronic data in the system used to create it; copies of electronic files outside the active system;
- Any use of electronic files should include consideration of ensuring appropriate computer hardware/software retention to ensure ongoing access to the data in human readable form;
- Where and how will they be kept? Document storage locations need to be identified and appropriately equipped to ensure records are protected from damage by fire, water, humidity or rodents. They should be secure with limited personnel access;
- For longer term storage, contract archive might be beneficial. If this is used, then the facility should be subject to periodic audit and a

technical/quality agreement should be in place. The technical/quality agreement should cover arrangements for rapid retrieval of records in the event of an audit/regulatory inspection or complaint/recall;
- Who will be responsible for them?
- How will they be indexed so that they can be located and retrieved promptly?

Since these GDP guidelines were written, there has been a significant volume of additional regulatory guidance relating to data integrity – see Bibliography. Be aware of these and ensure that your activities meet the 'ALCOA+' expectations:
- Attributable – it is easy to ascertain who created, approved or changed a record
- Legible – applicable to all records, including those that have been changed
- Contemporaneous – entering data directly and at the time of operation reduces risk of error arising from lapses of memory or transcription
- Original - original (or true copy) records are retained and available as evidence in an enduring (permanent) medium
- Accurate - which includes completeness and consistency

Specifics for instructional documents
These documents exist for the use of personnel and therefore need to be in a language understood by them. They are expected to be typed, not hand-written, to avoid any errors caused by difficulties with reading another person's handwriting.
To aid clarity:
- Short, directive statements ('do this', 'record that', etc.) in numbered steps are preferable to long prose;
- Consider use of process flow maps, diagrams or photographs – "a picture tells a thousand words";
- Instructions should match the order in which the operation or activity will be carried out;
- A 'house style' will help, especially where operations involve multiple documents;
- Make sure those expert in performing the activity are directly involved in the writing and review of documents;

To facilitate use:
- Locate procedures and work instructions in the workplace, with enough copies and/or terminals available in larger facilities, to enable staff to readily access them
- Create templates for records that need to be made;
- If handwritten entries are required, allow sufficient space to allow them to be made completely and legibly.

Document approval
- Procedures are required to be approved by the Responsible Person to ensure that they have full oversight of the quality system and its fitness for purpose. It is not only procedures that the RP needs to approve. See EU GDP Guideline 2.2;
- Various other documents might be approved by line management instead of, or in addition to, the RP;
- In all cases, the person(s) approving a document should have appropriate knowledge to ensure that activities are undertaken correctly.

Changes to documents
- Legislation and best practice expectations change over time and it is good business practice to have a continuous improvement philosophy, so procedures should be reviewed periodically and updated as required;
- Although the guideline only explicitly mentions version control in relation to procedures, it is likely to be beneficial to also apply this practice to other documents e.g. templates used for making records;
- Version control includes a unique number or code with effective date, revision date and version number. This enables clarity regarding which document was current at the time a given activity was performed;
- A standardised template can help significantly where there are similar types of documents e.g. SOPs, work instructions;
- A section for document history is helpful to detail what changes were made for each version number update;
- The procedure system should include a process for training and competence assessment ahead of a new version becoming effective, but it should also be ensured that staff do not change their working practices prior to the effective date of the new version;
- To prevent inadvertent use of superseded procedures:
  - Develop a system, and assign specific individual(s) responsibilities to ensure that superseded versions of paper copy procedures are removed from workstations and replaced with the new version in a timely manner;
  - Where electronic procedures are used, only the current version should be available to users; access to previous versions should be limited to document management staff;
  - If it is possible to print procedures from an electronic system, then ensure staff do not keep personal printouts of these. Training in a new version should include a reminder about this and checks should be carried out during self-inspections. Consideration should be given to preventing printing if it can be assured that staff will have access to terminals at point of operation. Alternatively, consider automatic addition of an expiry date at the time of printing and/ or recording printing and requiring staff to confirm destruction of printouts.

Specifics for records
Signing and dating documents ensures that there is clarity regarding who performed the activity and when. Note that signing and dating may be by electronic means as well as 'pen on paper'.

Where records are made by hand the 'sufficient space' requirement helps to ensure legibility and completeness – reducing the risk of a record being incomplete because the individual could not capture everything in the available space and had nowhere else to record additional details.

If paper records are made, provide specific locations in each work area where these can be safely and conveniently kept while operations are in progress.

Changes to entries
To maintain data integrity and enable trace back and understanding of any changes made, changes made to paper records should be made as follows:

- Strike through the original entry with a single line ensuring the original (incorrect) information is still legible;
- Sign (or initial) and date next to the strike through (a standard, unambiguous (i.e., not digits only), date format should also be specified in procedures);
- Provide a reason for the error/changed entry (e.g., 'transposition error'; 'date error', 'incorrect entry field'), either next to the correction or in a clearly referenced foot or margin note.

Note (1): Some companies specify codes that may be used in their documentation procedure (e.g., 'TE' = 'transcription error'); this can save time and space, but there is an increased risk of ambiguity if a code is used rather than writing in full.
Note (2): It is best practice to always write a reason, even if it may appear obvious at the time.

Changes made by over-writing or use of a 'white out' product do NOT comply with GDP requirements and staff should be trained that such practices are not acceptable.

To provide an equivalent control of changes within electronic systems, they should have an 'audit trail' functionality which captures a record of 'before' and 'after' entries in each 'data cell' together with a time/date stamp and identification of the individual logged in to the terminal at which the change was made.

Chapter 5 – Operations

5.1. Principle

All actions taken by wholesale distributors should ensure that the identity of the medicinal product is not lost and that the wholesale distribution of medicinal products is performed according to the information on the outer packaging. The wholesale distributor should use all means available to minimise the risk of falsified medicinal products entering the legal supply chain.

All medicinal products distributed in the EU by a wholesale distributor must be covered by a marketing authorisation granted by the EU or by a Member State [(1)].

Any distributor, other than the marketing authorisation holder, who imports a medicinal product from another Member State must notify the marketing authorisation holder and the competent authority in the Member State to which the medicinal product will be imported of their intention to import that product [(2)]. All key operations described below should be fully described in the quality system in appropriate documentation.

(1) Article 76(1) and (2) of Directive 2001/83/EC.

(2) Article 76(3) of Directive 2001/83/EC.

5.2.Qualification of suppliers

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 [(3)].

(3) Article 80(b) of Directive 2001/83/EC.

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 [(4)].

(4) Article 40, third paragraph of Directive 2001/83/EC.

Where medicinal products are obtained from another wholesale distributor, the receiving wholesale distributor must verify that the supplier complies with the principles and guidelines of good distribution practices and that they hold an authorisation for example by using the Union database. If the medicinal product is obtained through brokering, the wholesale distributor must verify that the broker is registered and complies with the requirements in Chapter 10 (5).

(5) Article 80, fourth paragraph of Directive 2001/83/EC.

Appropriate qualification and approval of suppliers, should be performed prior to any procurement of medicinal products. This should be controlled by a procedure and the results documented and periodically rechecked.

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

What is the rationale for this point of guidance?
These points are largely reminders of legislative requirements intended to minimise the risks of:

- Falsified medicines entering the supply chain;
- Products not being maintained (stored and transported) to appropriate GDP standards, thus impacting quality.

Wholesale distributors have a key role in safeguarding the supply chain of medicinal products and a fundamental part of this is to ensure that products are obtained from legitimate sources – the manufacturer or another authorised wholesale distributor.

Where products are sourced from outside the European Union (EU), there is a requirement for a Qualified Person (QP) to certify that they have been manufactured and checked in accordance with EU Good Manufacturing Practice (GMP) legislation and so a manufacturing authorisation (on which the QP is named) must be held.

The Falsified Medicines Directive (FMD, 2011/62/EU) introduced new requirements around the brokering of medicinal products – the negotiation around sale or purchase of products without physically handling them – including the registration of brokers. The GDP Guideline has subsequently provided specific provisions relevant to brokers in Chapter 10.

Complying with these requirements will safeguard against risks that might be associated with receipt of goods:

- Without appropriate documentation that assures complete audit trail;
- Prior to Qualified Person (QP) certification, which ensures that products are of appropriate quality and comply with their marketing authorisation;
- Labelled in the wrong language for the intended customer;
- Subject to recall;
- With inadequate shelf life remaining to enable onward supply to customers.

Issues with a supplier can impact business efficiency and reputation. So, for both regulatory and business reasons, a written procedure should be in place for supplier approval and records kept of the assessments leading to these approvals. Periodic re-evaluation helps to ensure on-going compliance and safeguards against the use of a supplier who has been found to have significant GDP deficiencies or is no longer authorised.

Implementation
If products are to be sourced from outside the EU, then a manufacturing authorisation must be obtained and associated requirements followed (these are outside the scope of this GDP guidance). A Qualified Person (QP) will need to be employed and named on the authorisation. The QP for a company sourcing products from outside the EU should have a good understanding of the GMP and GDP requirements in the source country and how these compare with EU requirements.
The primary requirement is to have a procedure for the appropriate qualification and approval of suppliers. Adherence to this procedure should be ensured for all suppliers, including brokers, and the resultant documents kept since these may need to be provided to regulatory inspectors and third party auditors.

The initial supplier approval should include appropriate 'due diligence' checks. These will look, not only at GDP-specifics, such as appropriate legal authorisations (as per member state procedures), quality systems, and capability and competence relevant to the products being supplied, but also at matters such as financial strength and searches for any legal action taken against the supplier.

Subsequent periodic re-evaluations and approvals should ensure that, as a minimum, the legal authorisation has been maintained and that service has been in line with agreements. The re-evaluation period should be defined based on risk assessment; an annual re-evaluation is recommended initially.

Use of the EudraGMDP database is recommended as a secure source of information. This holds details of current Wholesale Distributor Authorisations (WDA) and both GDP certificates and non-compliance reports.

Note: The UK MHRA has stated (2014) that any depot, freight consolidator or freight forwarder which holds stock in either ambient or cold room conditions for more than 36 hours must be licenced. Consult your local competent authority to clarify the requirements in your country.

Registers of brokers are maintained by the national competent authorities. Not all member states currently publish such a list, but it is intended that this should be the case in the near future.

For the UK, the list of registered brokers may be found on the MHRA website (see Bibliography for url).

A mechanism should be in place to promptly detect any loss of authorisation of suppliers. Availability of this information will depend on national competent authority processes. In the UK, the MHRA issue an updated list monthly, which is available from their website and it is possible to sign up for email notifications of updates.

In addition to assessing the suitability of suppliers in terms of their compliance, appropriate technical/quality agreements should be put in place before using them.

Agreements should include:

- Arrangements to allow for audits;
- Arrangements for the communication of outcomes of regulatory inspections;
- Arrangements for the communication and handling of complaints and recalls;
- Details of any quality critical aspects specific to the products to be supplied;
- Suitable Key Performance Indicators (KPIs) to enable performance to be monitored.

Procurement procedures and training of relevant staff should include points (ii) to (iv) of the EU Guideline as part of the ongoing vigilance against the introduction of falsified products into the supply chain. Remember the old adage about an offer that seems too good to be true! Prices may vary from time-to-time and market-to-market, but products which are offered at below market prices should be viewed as suspect.

5.3 Qualification of Customers

Wholesale distributors must ensure they supply medicinal products only to persons who are themselves in possession of a wholesale distribution authorisation or who are authorised or entitled to supply medicinal products to the public.

Checks and periodic rechecks may include: requesting copies of customer's authorisations according to national law, verifying status on an authority website, requesting evidence of qualifications or entitlement according to national legislation.

Wholesale distributors should monitor their transactions and investigate any irregularity in the sales patterns of narcotics, psychotropic substances or other dangerous substances.

Unusual sales patterns that may constitute diversion or misuse of medicinal product should be investigated and reported to competent authorities where necessary. Steps should be taken to ensure fulfilment of any public service obligation imposed upon them.

What is the rationale for this point of guidance?

As with the steps taken to qualify suppliers, the requirement to qualify customers is part of the wholesale distributor's role in safeguarding the supply chain of medicinal products. By ensuring that they only supply to appropriately authorised persons, wholesale dealers help to maintain a reliable 'chain of custody' to the patient and reduce the risk of products being misdirected and/or misused.

It is important that there are periodic rechecks because authorisations may change over time.

Wholesalers may be able to detect unusual sales patterns that might indicate illegal activities which would not otherwise be identified.

If products are provided to customers other than those authorised to receive them, then patients may be put at risk through:

- Incorrect storage or transportation impacting product stability, and thus suitability for use;
- Lost traceability, affecting the ability to recall a specific batch of product if required;
- Product tampering;
- Product sales without the safeguards of a prescription from a medical practitioner or supervision from a pharmacist;
- Products sold for purposes other than those legally permitted.

Implementation

Local procedure(s) should be put in place to address these requirements defining:

- How bona fides of customers are established before they can be accepted as customers. This would include not only the submission of documentary evidence from the customer, but also independent checks on competent authority or professional regulator databases. With the exception of the EudraGDMP database for EU WDA holders, these are likely to be national and vary from country to country, so contact your local Competent Authority for advice;

- Additional checks that may be appropriate to customers of controlled substances;
- The need to identify and adhere to any limitations regarding the supply of products to a given customer;
- Triggers for periodic re-evaluations and the process for conducting these (this could be by time, number of orders or even on each order, depending on customer history and/or product);
- What might constitute an 'unusual sales pattern' and how sales will be monitored for these;
- How potential issues should be flagged first of all to company management and then to competent authorities as appropriate.

5.4 Receipt of medicinal products

The purpose of the receiving function is to ensure that the arriving consignment is correct, that the medicinal products originate from approved suppliers and that they have not been visibly damaged during transport.

Medicinal products requiring special storage or security measures should be prioritised and once appropriate checks have been conducted they should be immediately transferred to appropriate storage facilities.

Batches of medicinal products intended for the EU and EEA countries should not be transferred to saleable stock before assurance has been obtained in accordance with written procedures, that they are authorised for sale. For batches coming from another Member State, prior to their transfer to saleable stock, the control report referred to in Article 51(1) of Directive 2001/83/EC or another proof of release to the market in question based on an equivalent system should be carefully checked by appropriately trained personnel.

What is the rationale for this point of guidance?

Receipt checks are an important part of maintaining a reliable 'chain of custody' to the patient, providing assurance that:

- The supplier is authorised;
- The product is as ordered and is authorised for sale;
- The product has not been tampered with or visibly damaged;
- The product has been, and is, maintained under the correct storage conditions; as defined on the label; see Chapter 9 for guidance on the management of excursions.

Risks associated with inadequate receipt processes include:

- Products coming from unauthorised sources, which as well as being a compliance issue increases the risk that they might be falsified;
- Products not being transported under appropriate storage conditions or not being promptly transferred into appropriate storage following receipt, thus impacting product stability.

There may be additional risks associated with particular products, requiring 'special arrangements' to be in place to handle them, for example cold chain products or controlled drugs (e.g., narcotics). Whenever 'special arrangements' are required, there are added risks that these arrangements will not be followed due to lack of resource, training or human error.

Large volume receipts, or multiple receipts in a short time period, can stress resources available to handle receipts and consideration should also be given to the risk of storage capacity being exceeded.

Benefits of a good receipt process include:

- Assurance of the 'chain of custody', providing confidence to customers and enabling recall if required;
- Prompt detection of any issues with the received material, such as tampering, physical damage or incorrect storage;
- Confidence that materials invoiced have actually been received;
- Confidence during regulatory inspections.

Implementation

Whilst appropriate checks on arriving consignments are essential, certain elements of receipt are actually best dealt with as part of the ordering process and/or agreements with suppliers. For example, ensure that there is ready access to certificates of analysis and/or certificates of compliance (conformance), either through documentation to be sent with each shipment or through provision in other ways, such as via the supplier's website. Furthermore, arrangements such as the provision of an Advance Shipping Notice (ASN) with details of lot number, expiry date and SSCC (Serial Shipper Container Code*) number can facilitate quick and easy receipt checking.

*A SSCC is an 18-digit code in a GS1 barcode format or radio frequency identification (RFID) tag which identifies the manufacturer/supplier and packaging unit.

A receipt procedure should be in place which includes the following:

- Confirmation that the supplier is approved;
- Confirmation that the goods are as ordered (Delivery Note check against Purchase Order);
- Confirmation that the goods are as stated (check physical stock identification, quantities, batch numbers and expiry dates against Delivery Note);
- Confirmation of territories for which the product is authorised for sale;
- Confirmation that the received material has not been damaged or

tampered with
- Confirmation that the received material has been transported under appropriate storage conditions;
- Arrangements for booking the received material into inventory;
- Arrangements for ensuring the material is promptly transferred to appropriate storage;
- Any particular national arrangements, e.g., for samples to be taken and retained;
- Any special arrangements for certain types of product.**

**Note that whilst all medicinal products should be stored under appropriate conditions to avoid deterioration, some require tighter controls and may therefore require special arrangements, e.g., vaccines may have very limited stability outside 2 - 8°C. Some products may have very short shelf life (e.g., 'Specials' ordered for specific patients). Certain classes of product (typically those of high value) may be more susceptible to falsification and others may be subject to additional legal restrictions and controls. All of these may require arrangements over and above those for more 'standard' products.

As with other elements of GDP, staff training and assessment of competence is important.

Careful facility and capacity planning is required to ensure adequate volumes of the required types of storage. Systems need to be in place to check storage capacity prior to ordering and delivery times may need to be staggered to smooth out the workload.

A specific cold store (or segregated area within a cold store) for incoming materials will enable appropriate storage conditions to be maintained whilst receipts are processed.

Ensure that the specific storage requirements for each product are readily identifiable on the delivery documentation.

Aim to separate product flows according to storage requirements (e.g., avoid 'room temperature' products being placed in cold stores).

The 'control report' referred to in Article 51(1) of Directive 2001/83/EC is the document signed by the Qualified Person at the manufacturing site which declares the marketing authorisation against which the batch has been certified. Agreements with suppliers should ensure that a copy of this document is provided with each batch.

The receipt procedure should ensure that documents, including temperature records, are readily available to allow rapid review by the Responsible Person or other appropriately trained staff.

A procedure should also describe how to ensure that batches of product are only transferred into saleable stock (available for picking to fulfil customer orders) after all relevant associated documents have been reviewed and deemed satisfactory.

Archive freight documents promptly so that they can be accessed at a later date if required.

5.5 Storage

Medicinal products and, if necessary, healthcare products should be stored separately from other products likely to alter them and should be protected from the harmful effects of light, temperature, moisture and other external factors. Particular attention should be paid to products requiring specific storage conditions.

Incoming containers of medicinal products should be cleaned, if necessary, before storage.

Warehousing operations must ensure appropriate storage conditions are maintained and allow for appropriate security of stocks.

Stock should be rotated according to the 'first expiry, first out' (FEFO) principle. Exceptions should be documented.

Medicinal products should be handled and stored in such a manner as to prevent spillage, breakage, contamination and mix-ups. Medicinal products should not be stored directly on the floor unless the package is designed to allow such storage (such as for some medicinal gas cylinders).

Medicinal products that are nearing their expiry date/shelf life should be withdrawn immediately from saleable stock either physically or through other equivalent electronic segregation.

Stock inventories should be performed regularly taking into account national legislation requirements. Stock irregularities should be investigated and documented.

What is the rationale for this point of guidance?

To safeguard products from environmental factors that might impact their stability or other quality parameters that would render them unsuitable for use, e.g., packs with faded text or carrying an odour. Storage of products

according to labelled storage conditions, maintains their stability over their full shelf life.

Environmental factors can create a number of risks if not adequately controlled:

- Light: Can cause physical discolouration of product or printed components and certain products may be susceptible to light-catalysed chemical degradation. Product development activities should include packaging providing appropriate light protection, but issues can still be caused by exposure to strong artificial light sources or sunshine;
- Temperature: Chemical degradation increases as temperature increases and some products, such as suppositories (which can melt), creams (which can separate) and suspensions (which can flocculate), may have their physical stability impacted by either high or cycling temperatures. Most product packaging has minimal thermal insulation relying on control of the environment to prevent products being exposed to adverse temperatures. Liquid products may also be susceptible to freezing;
- Moisture: If products are exposed to excess water vapour then they can be susceptible to hydrolytic degradation or physical deterioration. As with light, product development activities should result in appropriate packaging systems, possibly including a desiccant, to protect from humidity, but these can be overloaded if high humidity is maintained over a long period of time. Cartons and labels may also be susceptible to damage by prolonged high humidity;
- Other external factors: These could include strong odours or spilled chemicals which could have direct impact on products or their packaging rendering them unsuitable for use.

In some cases, degradation of product or packaging will be readily apparent to the recipient resulting in complaints. In other cases, the fact that the product is not suitable for use may not be apparent to the end user and could result in adverse effects on their health.

Good environmental control will assure product suitability for use throughout the stated shelf life.

Cleaning incoming containers reduces the risk of contaminating the warehouse and stored products with dust, debris or insects and is important because:

- Any dust/ debris which is not removed could subsequently be transferred to the patient pack during picking, which would undermine recipient confidence in the medicine, resulting in additional returns and thus increased workload;
- Additional work is created if the warehouse becomes infested by insect or other pests.

Warehouse security arrangements safeguard products from:

- Humans who might damage, tamper with or pilfer them, leading to direct patient harm, falsification activities and/or business losses;
- Pest animals, insects and birds that can damage or soil products, rendering them unfit for use.

Products should not be stored directly on the floor since they are then more likely to become damaged or contaminated by spillages, water and/or pests, rendering them unfit for supply.

Spillage, breakage and contamination can lead to product exposure creating a potential health and safety risk to staff or customers.

Supply of damaged or incorrect products to customers will result in complaints and damage to reputation.

FEFO arrangements ensure that product is supplied in a controlled manner and that shortest expiry dated product is placed into the market first. This reduces business overheads from wastage and the additional work and cost associated with returns. It also helps to maintain efficient supply of product to patients ensuring that end users have sufficient remaining shelf life.

Exceptions are necessary for customers who request a specific batch size/ quantity to be supplied. Other exceptions might occur where the supplied product is intended to be used as a starting material for further manufacture, such as preparing blinded investigational medicinal products, and the customer therefore requests supply with product carrying the longest possible expiry date.

If customers deem remaining shelf life to be too short, a complaint/return for replacement is likely. This is inefficient for both supplier and customer and could result in patients experiencing delays receiving medicines they need.

Regular inventory checks provide assurance that product has not been lost or unaccountably gained. This provides confidence in warehouse systems and the ability to meet orders. Irregularities could be the result of under/over-picking, theft or misplacement in the warehouse. Investigation of irregularities can identify issues with warehouse systems for improvement. More seriously, investigations could uncover criminal activity – theft or the introduction of falsified products.

Implementation

Storage facilities should be designed, validated, maintained and operated in order to provide appropriate product protection:

- Products should not be stored in areas exposed to strong artificial or sun light – sky lights should be avoided and artificial lights should be 'low energy'; if strong artificial lights are needed, then additional protection may be required for products stored nearby;
- The facility should have sufficient capacity of temperature-controlled storage areas appropriate to the label storage conditions of the different products handled
- Receipt procedures should ensure that products are promptly located to the correct storage areas based on their label storage conditions;
- Storage facilities should be temperature mapped to identify any hot or cold spots (and thereafter avoiding storage of thermally sensitive products in such zones);
- Storage facilities should be subject to 'continuous' temperature monitoring with temperatures being captured from calibrated probes in representative and 'worst case' (hot and cold spot) locations. It is recommended that data are captured at least every 15 minutes;
- Alarms should be set at appropriate temperature limits and procedures should cover actions to be taken promptly in the event of an alarm being triggered
- The storage facility should prevent the entry of rain and should be well ventilated to prevent humidity build up. Humidity control may be required in certain local climates;
- Procedures should be in place to rapidly deal with any spillages to prevent contamination of stored products;
- If possible, the storage area should be dedicated to medicinal products. If other chemicals or food products are stored in the same facility, then consideration should be given to the potential for odour contamination. Strong-smelling items should be segregated from medicinal products;
- In the event that fumigation is required to deal with an infestation, product should be removed prior to the procedure to prevent chemical contamination and very carefully inspected prior to return to avoid reintroducing the infestation;
- Storage areas should be well-built and secure with access restricted to appropriate company personnel;
- Procedures and staff training should ensure that entry points are securely closed at all times when not in active use;
- Security cameras should be located to cover entrances; internal cameras should also be considered, especially for areas used for high value products or controlled drugs;
- A 'right of search' should be established and periodic random searches should be conducted of staff leaving the premises;
- A comprehensive pest control programme should be in place and maintained. See Section 3.2(vii);
- Procedure and racking/pallet system should require/enable products to be stored off the floor. This can be reinforced by clear signage and staff training. Computerised inventory systems should not include the floor as a possible location.

Include expectations for delivery which help to ensure minimal contamination, e.g., shrink/stretch wrapping of pallets, in Technical/Quality Agreements with suppliers together with the right to refuse delivery or to charge for cleaning if these expectations are not met.

The receipt procedure should include checks for cleanliness and light wiping of dusty boxes prior to placement in store. Any received materials requiring more than a light wiping away of dust should be referred to relevant management to determine if agreed terms and conditions have been broken. Capturing photographic evidence is recommended if complaint is to be made.

Use of a validated computerised inventory system with FEFO rules forming part of the picking module is probably the best way to ensure compliance with this guidance. It should be possible to override the automatic selection to enable exceptional circumstances to be met.

Smaller organisations using manual inventory control systems will need to put a process in place to review the batches of product held and ensure that the batch with lowest shelf life is picked first to meet an order.

Inventory checks carried out for accounting purposes and/or self inspections should be used to confirm that the FEFO process is operating effectively.

Assigning specific locations for the storage of any highly active products might be beneficial. A similar approach is recommended for large volume bottled liquids.
Regularly inspect areas to confirm that products are stored appropriately.

Agree and implement a policy on the minimum acceptable remaining shelf life (for each product) for both received and issued stock. Include these limits into both the receiving and issuing stock control systems, regardless of whether they are computerised or manual. A procedure should be in place to describe the process used to maintain the minimum shelf life acceptable for each product, and how to update the inventory system.

Note: In defining this limit, consider product stability, availability and utilisation. For example, a shorter remaining shelf life may be acceptable for antibiotics, which are prescribed frequently and normally only used for a short period of time, than for rescue/reliever inhalers for asthmatics, which might be held by patients for long periods of time, for use 'as needed'.

Inventory control:

- Define acceptable tolerances, based on quantity and not on value;
- Introduce a regular programme of stock checks;
- Ensure that stock checks happen as planned;
- Ensure that significant stock irregularities are documented and communicated to management for review and further action as appropriate;
- A validated IT system can help to provide controls that reduce the risk of inventory errors;

5.6 Destruction of obsolete goods

Medicinal products intended for destruction should be appropriately identified, held separately and handled in accordance with a written procedure.

Destruction of medicinal products should be in accordance with national or international requirements for handling, transport and disposal of such products. Records of all destroyed medicinal products should be retained for a defined period.

What is the rationale for this point of guidance?

This guidance ensures that:

- Products intended for destruction do not inadvertently enter the supply chain for patient use or become diverted;
- Destruction takes place in a suitable, controlled, manner that minimises the environment, health and safety risks;
- A full audit trail exists in the event that there is a need to investigate a batch history.

Implementation

- Have a written procedure for handling products intended for destruction and train staff;
- Inventory systems, whether manual or computerised, should clearly indicate when stock is assigned to be destroyed and record the actual destruction;
- Computerised systems should be validated to prevent stock assigned for destruction being allocated to orders;
- With manual systems, 'stock cards' should be flagged and ideally moved so that they are not visible to staff allocating stock to orders;
- Physical labelling of boxes or pallets of material for destruction and moving them to a secure, dedicated and designated area will provide additional assurance against inadvertent picking;
- Having locks on this designated area provides an additional barrier to both inadvertent picking and theft;
- Certificates of destruction should be reconciled with records of materials sent for destruction;
- Understand national and international requirements for handling, transport and disposal of medicinal products;
- Be aware of and appropriately communicate the hazards associated with each product handled;
- Be aware of and follow special requirements for controlled drugs (narcotics) and high value products;
- Use only certified contractors for destruction;
- Audit contractors used for destruction prior to appointment and periodically thereafter (every 2-3 years would be typical) to ensure that the appropriate facilities, equipment and processes are in place and maintained;
- Have written agreements in place with contractors used for destruction clearly stipulating their responsibilities for secure and safe operations and the provision of appropriate documentation;
- Certificates of destruction should detail product, batch number and quantity and should be promptly archived for a defined period of time.

5.7 Picking

Controls should be in place to ensure the correct product is picked. The product should have an appropriate remaining shelf life when it is picked.

What is the rationale for this point of guidance?

The picking and checking process determines what and how much product is sent to the customer. If the process is not robustly controlled, then complaints will result from customers not receiving what they have ordered. Likewise, complaints will be received if the customer is not satisfied that there is sufficient remaining shelf life on the products received. A robustly controlled picking process will prevent complaints arising from errors.

Implementation

The main risk associated with picking is a failure to check all elements of the product's identity, e.g., just looking at the name and selecting a different strength, dosage form or pack size. Ensure that staff are aware of all elements of a product's identity relevant to delivering what the customer has ordered, e.g.:

- Trade name;
- Dosage form (tablet, capsule, suspension, etc.);
- Strength (dose);
- Quantity per pack / pack Volume / size;
- Pack language / intended market.

As detailed in Section 5.5, agree and implement a policy on the minimum acceptable remaining shelf life (for each product) for issued stock and build a check for compliance into the process; follow FEFO principles unless an exception is agreed.

Where possible, make use of validated electronic systems to allocate materials and facilitate their picking. Use the system to allocate the stock to be picked according to FEFO principles with validation of remaining shelf life; Scan the barcode on each container picked for the consignment to check that what has been picked matches the allocation and flag an error message if this is not the case.

5.8 Supply

For all supplies, a document (e.g. delivery note) must be enclosed stating the date; name and pharmaceutical form of the medicinal product, batch number at least for products bearing the safety features; quantity supplied; name and address of the supplier, name and delivery address of the consignee [7] (actual physical storage premises, if different) and applicable transport and storage conditions. Records should be kept so that the actual location of the product can be known.

(7) Article 82 of Directive 2001/83/EC.

What is the rationale for this point of guidance?

A delivery note ensures that:

- The driver knows where to deliver the ordered product(s) and to whom;
- The recipient can check the delivery against the order;
- The recipient is aware of and able to confirm the transport and storage conditions, checking for any deviation during transport and ensuring appropriate storage following receipt;
- There is a record of 'chain of custody' in the event of a recall or other issue and the risk of falsification is reduced.

Implementation

- A standard delivery note template with all the required information fields should be used;
- The delivery note should be used by the recipient to check that:
  - goods received are those that have been ordered;
  - products have been transported under appropriate conditions.

5.9 Export to Third Countries

The export of medicinal products falls within the definition of 'wholesale distribution' [8]. A person exporting medicinal products must hold a wholesale distribution authorisation or a manufacturing authorisation. This is also the case if the exporting wholesale distributor is operating from a free zone.

The rules for wholesale distribution apply in their entirety in the case of export of medicinal products. However, where medicinal products are exported, they do not need to be covered by a marketing authorisation of the Union or a Member State [9]. Wholesalers should take the appropriate measures in order to prevent these medicinal products reaching the Union market.

Where wholesale distributors supply medicinal products to persons in third countries, they shall ensure that such supplies are only made to persons who are authorised or entitled to receive medicinal products for wholesale distribution or supply to the public in accordance with the applicable legal and administrative provisions of the country concerned.

(8) Article 1(17) of Directive 2001/83/EC.

(9) Article 85a of Directive 2001/83/EC.

What is the rationale for this point of guidance?

These points are largely reminders of legislative requirements intended to ensure that all products passing through EU-based wholesale distributors are protected by EU GDP standards irrespective of their intended market. This helps to safeguard global supply chains. They also ensure that only products with an EU marketing authorisation reach the EU market, assuring that EU patients receive products meeting EU regulatory standards.

Implementation

EU based wholesale dealers should:

- Work to a single standard of GDP which meets EU requirements, irrespective of where products are going to be supplied;
- Implement procedures to ensure that products are only supplied to markets where they are authorised, or to other wholesale dealers. Including market details within the inventory descriptions can be useful;
- Apply the guidance in Section 5.3 to the qualification of customers wherever they are based.

Chapter 6 – Complaints, Returns, Suspected Falsified Medicinal Products & Medicinal Product Recalls

6.1 Principle

All complaints, returns, suspected falsified medicinal products and recalls must be recorded and handled carefully according to written procedures. Records should be made available to the competent authorities. An assessment of returned medicinal products should be performed before any approval for resale. A consistent approach by all partners in the supply chain is required in order to be successful in the fight against falsified medicinal products.

Introduction to this section in the guidance

Routinely, there is a one-way flow of product through the distributor from supplier to customer and no further action is required by the distributor once the goods are received by the customer. Occasionally, however, there may be complaints that need to be dealt with or a customer may wish to return a product. Rarely, there may be suspected falsified medicinal products or product recalls. All these situations require careful handling to safeguard both patients and the business. To ensure appropriate handling, clear written procedures are required. All actions taken must be carefully recorded with the resulting documentation retained.

6.2 Complaints

Complaints should be recorded with all the original details. A distinction should be made between complaints related to the quality of a medicinal product and those related to distribution. In the event of a complaint about the quality of a medicinal product and a potential product defect, the manufacturer and/or marketing authorisation holder should be informed without delay. Any product distribution complaint should be thoroughly investigated to identify the origin of or reason for the complaint.

A person should be appointed to handle complaints and allocated sufficient support personnel.

If necessary, appropriate follow-up actions (including CAPA) should be taken after investigation and evaluation of the complaint, including where required notification to the national competent authorities.

What is the rationale for this point of guidance?

Complaints may relate to the quality of the product or of the distribution service. A robust system for recording complaints, differentiating between the two types, will ensure appropriate action is promptly taken. The nature of the corrective / preventive actions can be very different in each case. All product-related complaints should be rapidly referred to the Marketing Authorisation Holder (MAH). Service complaints are typically the responsibility of the Wholesale Dealer's Authorisation (WDA) Holder. Each complaint is valuable feedback from the customer and a useful input to quality improvement activities.

A failure to deal effectively with product-related complaints could result in risks to patients if similarly affected poor quality product enters or remains in the supply chain and/or the MAH is not made aware of adverse events in a timely manner.

A failure to deal effectively with service-related complaints could result in:

- Continued poor service compared to the competition
- Stock issues if incorrect quantities are sent out.

Given the importance of the complaint process, a defined individual is expected to have accountability for it and needs to be given sufficient resources to ensure that all required activities, such as entering complaints into the system, analysing data, investigation and agreement on preventive/corrective actions, are completed in a timely manner.

Implementation

The following need to be in place as a minimum:

- Appointment of a suitably experienced person to manage complaints, e.g. the Quality Manager or RP, with appropriate resources available for this activity;
- Robust procedure(s) for managing all complaints, including the following:
  - Capture of all relevant details of every complaint (it is best practice to log and investigate all complaints received and determine validity later, rather than to pre-judge whether a complaint is justified or not). Pre-formatted forms or checklists can help ensure this;
  - Thorough assessment of each complaint, including the identification of root cause(s) and appropriate CAPAs, capturing these details in a formal report;
  - RP review and approval of each complaint report;
  - Defined contacts internally and with MAHs and Health Authorities to ensure effective communication channels;
  - A process to ensure the timely completion of identified and agreed CAPA;
- Appropriate staff training (initial and periodic refresher):
  - All personnel should be trained to understand what a complaint is, what to do when receiving a complaint and the importance of rapid

communication and correct 'routing';
- Specific training is required for personnel in contact with customers (e.g. sales people, home delivery personnel) who may be the first to hear about a complaint;
- Detailed training is required for those involved in the investigation of complaints;

- Defined, appropriate performance indicators for the complaint process, regularly discussed at management review meetings with actions taken when necessary. Examples might include:
  - Number of complaints per sale or delivery;
  - Percentage of complaints closed later than a defined timeline;
  - Number of actions from complaints in "open" status.

6.3 Returned medicinal products

Returned products must be handled according to a written risk-based process taking into account the product concerned, any specific storage requirements and the time elapsed since the medicinal product was originally dispatched. Returns should be conducted in accordance with national law and contractual arrangements between parties.

Medicinal products which have left the premises of the distributor should only be returned to saleable stock if all of the following are confirmed:

(i) the medicinal products are in their unopened and undamaged secondary packaging and are in good condition; have not expired and have not been recalled;

(ii) medicinal products returned from a customer not holding a wholesale distribution authorisation or from pharmacies authorised to supply medicinal products to the public should only be returned to saleable stock if they are returned within an acceptable time limit, for example 10 days;

(iii) it has been demonstrated by the customer that the medicinal products have been transported, stored and handled in compliance with their specific storage requirements;

(iv) they have been examined and assessed by a sufficiently trained and competent person authorised to do so;

(v) the distributor has reasonable evidence that the product was supplied to that customer (via copies of the original delivery note or by referencing invoice numbers, etc.) and the batch number for products bearing the safety features is known, and that there is no reason to believe that the product has been falsified.

Moreover, for medicinal products requiring specific temperature storage conditions such as low temperature, returns to saleable stock can only be made if there is documented evidence that the product has been stored under the authorised storage conditions throughout the entire time. If any deviation has occurred, a risk assessment has to be performed, on which basis the integrity of the product can be demonstrated. The evidence should cover:

(i) delivery to customer;
(ii) examination of the product;
(iii) opening of the transport packaging;
(iv) return of the product to the packaging;
(v) collection and return to the distributor;
(vi) return to the distribution site refrigerator.

Products returned to saleable stock should be placed such that the 'first expired first out' (FEFO) system operates effectively.

Stolen products that have been recovered cannot be returned to saleable stock and sold to customers.

What is the rationale for this point of guidance?

Management of returned products is a major challenge for wholesalers. Products are returned for a variety of reasons; it may be that the wrong product or incorrect quantity was delivered or it may be that the customer has made an error or changed their mind regarding the goods ordered. Handling and storage of the product after dispatch might have resulted in physical damage, product degradation or contamination. There is also risk of the returns process being utilised to introduce falsified medicinal products into the supply chain. A risk-based assessment will facilitate decision making regarding whether to return product to saleable stock. To assist wholesalers in this risk assessment, the regulators have provided significant detail in this section. Appropriate procedures for handling returns will ensure compliance with national legislation and contractual arrangements, thus safeguarding the business, and, above all, protecting the public from the introduction of poor quality or falsified medicinal products into the supply chain.

Implementation

The guideline text contains significant detail which is not repeated here. These details should be incorporated into a clear, documented procedure with staff trained as appropriate to their roles. Checklists and/or decision trees may be helpful.

Ensure that returned products are stored in a separate, segregated and secure area, at the labelled storage conditions, so that they cannot enter the supply chain prior to completion of a proper assessment and decision on disposition and are protected from degradation.

If there is no evidence of the storage conditions, or there is evidence to suggest that the product has not been stored in accordance with the label conditions,

then the assessment should be referred to the MAH for a decision, unless the excursion is within acceptable parameters, as defined in the technical agreement.

In any case, product may only be returned to saleable stock if it is returned within an "acceptable time limit". It should be noted that whilst the guideline gives an example of 10 days, some regulators have published their own expectations in this regard. For example, the UK MHRA guidance suggests a maximum of 24 hours for refrigerated products and 5 days for other products returned from unlicensed sites.

The final decision regarding the disposition of returned product should be made by the Responsible Person, and should follow consultation with the MAH if required by the Technical Agreement or if they require advice. Any doubt about the authenticity or quality of the product will mean it is not approved for resale.

Clear, comprehensive record keeping will enable any emerging trends to be identified and used to continually improve.

6.4 Falsified Medicinal Products

Wholesale distributors must immediately inform the competent authority and the marketing authorisation holder of any medicinal products they identify as falsified or suspect to be falsified[1]. A procedure should be in place to this effect. It should be recorded with all the original details and investigated.

Any falsified medicinal products found in the supply chain should immediately be physically segregated and stored in a dedicated area away from all other medicinal products. All relevant activities in relation to such products should be documented and records retained.

(1) Article 80(i) 0f Directive 2001/83/EC

What is the rationale for this point of guidance?

Falsified medicines present a serious risk to public health; multiple deaths have resulted from such products which may contain no active ingredients, or active ingredients of poor quality and/or an incorrect dosage, or which have incorrect or contaminated ingredients. They will be deliberately and fraudulently mislabelled with respect to their identity or source and can be in fake packaging that is very difficult to distinguish from the genuine article. Extended (international) supply chains are especially vulnerable to such criminal activity and wholesale dealers are a potential source of entry for such products into the supply chain.

Ensuring that falsified medicines are kept out of the legitimate supply chain is an ongoing challenge. It is therefore imperative that all staff in the distribution chain are vigilant, helping to identify any falsified medicines received and so preventing them from being supplied to patients. Good communication with competent authorities (CA) and the MAH enables prompt action to be taken to mitigate further incidents.

Implementation

The following need to be in place as a minimum:

- Systems to ensure that purchase of medicinal products is always from a legitimate source by checking and monitoring the first time an order is placed, then at regular intervals thereafter. A range of means can be employed, including appropriate licence checks (bona fides), Quality Agreements and audits. Refer to Section 5.2 for further guidance;
- Mechanisms for obtaining evidence that the correct transport route has been followed to the storage site;
- Systems to ensure that products are only supplied to a bona fide customer; i.e. to check authorisations when orders are received from new customers and at regular intervals thereafter. Refer to 5.3 for further guidance;
- Training of staff to look out for warning signs of falsified products, such as quality of packaging / printing of components, differences/changes to packaging materials, and to compare suspect packs with known originals. Training using real examples, where possible, will reinforce understanding;
- A procedure which defines how the suspect / falsified medicine could be identified and what actions are to be taken. Details should include how and where the falsified product is segregated and stored from other products and communication process to the authorities and MAH.

6.5 Medicinal Product Recalls

The effectiveness of the arrangements for product recall should be evaluated regularly (at least annually).

Recall operations should be capable of being initiated promptly and at any time. The distributor must follow the instructions of a recall message, which should be approved, if required, by the competent authorities.

Any recall operation should be recorded at the time it is carried out. Records should be made readily available to the competent authorities.

The distribution records should be readily accessible to the person(s) responsible for the recall, and should contain sufficient information on distributors and directly supplied customers (with addresses, phone and/or fax numbers inside and outside working hours, batch numbers at least for

medicinal products bearing safety features as required by legislation and quantities delivered), including those for exported products and medicinal product samples.

The progress of the recall process should be recorded for a final report.

What is the rationale for this point of guidance?
Recalls are triggered if the MAH, in conjunction with the CA, deems there to be a significant risk to public health if a product remains on the market. Consequently, it is critical to ensure that systems are in place to enable prompt and effective action to be taken, even 'out of hours'. In the event of a recall, there needs to be clear communication and understanding of the roles and responsibilities of each party in the supply chain. Periodic evaluations enable assessment of the effectiveness of recall procedures and provide confidence in the personnel involved. Distribution records provide the basis for identification of specific customers receiving an affected batch. Documentation of each recall (real or simulated) provides evidence that appropriate actions have been taken and of their effectiveness, giving confidence to the distributor, their customers, MAHs and the CA.

Implementation
Formal notification of a medicinal product recall is made to the relevant pharmaceutical sectors by the CA in collaboration with the MAH. The CA will typically indicate in the notification the product details, the reason for the recall, and, based on the perceived potential hazard to patients, the classification, urgency and sectors to which the recall applies. The notification may also advise whether the product is to be returned to the original supplier or if it can be used with caution.

Distributors need to ensure the following are in place:

- Procedures describing how they will act following receipt of a recall communication from MAH/CA, and ensure that the instructions provided are followed.
    - The recall process should be managed and coordinated by a designated individual, who will typically be the Head of Quality or the RP.
- Resources enabling them to communicate directly with appropriate individuals at customer organisations, e.g., other wholesalers, hospitals, clinics, surgeries and retail pharmacies.
    - Evidence of communications should be retained providing records that customers have been contacted.
- Systems providing traceability of product movement.
    - Where manual systems are utilised, documentation should be legible and readily available.
    - All records should contain full product details for receipts, sales, returns, and adjustments for damages etc.
    - Where batch details are not available, all customers who have been supplied with the affected product form should be contacted and provided with the notification details.

The accuracy of records should be checked as part of the periodic effectiveness checks.

Chapter 7 – Outsourcing

A note about terminology
The GDP Guide uses the term 'Contract' for the written arrangements between the Contract Giver and Contract Acceptor. A number of different documents may make up the 'contract' covering both commercial and technical/ quality arrangements, e.g., 'Master Service Level Agreements'; 'Commercial Agreement'; 'Technical/Quality Agreements' or 'Quality and Technical Agreement' (QTA). For consistency, the term 'Contract' is therefore used in the ECA/PQG guidance and relates to both technical and quality arrangements of outsourcing.

7.1 Principle

Any activity covered by the GDP Guide that is outsourced should be correctly defined, agreed and controlled in order to avoid misunderstandings which could affect the integrity of the product. There must be a written Contract between the Contract Giver and the Contract Acceptor which clearly establishes the duties of each party.

What is the rationale for this point of guidance?
If either a contract is not prepared or the duties of each party are not clearly defined, then potentially serious errors will eventually occur to the detriment of both parties and possibly the end user (patient).

What are the benefits and risks associated with this point of guidance?
A clearly drafted contract which establishes the specific duties of each party (Contract Giver and Contract Acceptor) will benefit both parties significantly reducing the risk of adverse impacts on product or failures in supply with the associated potential for commercial loss.

The risks associated with failure to put such a contract in place are implicit.

Implementation
Companies engaged in outsourcing as Contract Givers should:

- Have a procedure detailing the activities and responsibilities which should be included in a contract;
- Discuss a draft Contract with potential Contract Acceptors before the commercial agreement is agreed by each party
  Note: it is quite common for more than one potential Contract Acceptor to be considered;
- Determine, and include within the Contract, the level of oversight to be exercised
  Note: this relates to the type and nature of events or information which would require referral or supply to the RP within the Contract Giver and also the intended frequency of audits.

Likewise, companies intending to be Contract Acceptors should have a procedure which ensures that their requirements are included in the Contract.

Both parties should ensure that the Contract is written, reviewed, approved and consistent with internal procedures, and that training is carried out prior to any work being outsourced if procedures have been changed
Both parties should ensure that the Contract is reviewed on a regular basis to maintain its currency.

An outline Contract for GDP outsourcing is given as Appendix 1 which provides additional guidance on required content. Every Contract Giver – Contract Acceptor arrangement is unique and the Contract should therefore be customised to work for both parties.

7.2 Contract Giver

The Contract Giver is responsible for the activities contracted out.

What is the rationale for this point of guidance?
This is a statement of the legal position of the Contract Giver.

What are the benefits and risks associated with this point of guidance?
Where responsibilities are not clearly understood, it may potentially lead to risk to product quality with consequent risk to the patient due to mistakes that could be made by the Contract Acceptor's staff.

Implementation
Contract Givers should have a QA system in place which monitors each Contract Acceptor to ensure that it performs its outsourced activities as defined in the contract.
This can be facilitated by:

- Agreeing each customer specific requirement with the Contract Acceptor, ideally during an initial face-to-face meeting;
- Arranging audits of the Contract Acceptor at regular intervals – see below.

7.2 Contract Giver

The Contract Giver is responsible for assessing the competence of the Contract Acceptor to successfully carry out the work required and for ensuring by means of the contract and through audits that the principles and guidelines of GDP are followed. An audit of the Contract Acceptor should be performed before commencement of, and whenever there has been a change to, the

outsourced activities. The frequency of audit should be defined based on risk depending on the nature of the outsourced activities. Audits should be permitted at any time.

What is the rationale for this point of guidance?
The Contract Giver retains responsibility for the activities contracted out. This clause provides further detail regarding the assessments that the Contract Giver is responsible for carrying out to ensure that the Contract Acceptor's systems, staff and facilities are fit for use. Such assessments should enable the Contract Giver to understand and mitigate risks associated with the outsourced activity.

The assessment of the suitability of the Contract Acceptor goes beyond initial selection and approval and should be a feature of the on-going relationship between the parties for the lifetime of the contract, so repeat audits should be undertaken at a frequency determined by the Contract Giver's risk assessment.

It should be agreed and stated in the Contract that audits could be carried out by the Contract Giver at any time if required, to permit, for example, a `for cause' investigation in the event of a serious complaint or problem arising.

What are the benefits and risks associated with this point of guidance?
Where the Contact Giver invests sufficient time to assess the key personnel, competence and culture of a potential Contract Acceptor, this will help build understanding of the Contract Acceptor's business and organisation which should facilitate future communications and help minimize potential problems.

Performing a thorough risk assessment requires a clear understanding of the full supply chain and should include specific details relating to all contractors and sub-contractors involved in storage, distribution or transportation. In today's global environment, risks are inevitably increased where supply chains are long and complex involving many steps, e.g. primary hubs and secondary depots, re-exporting, freight forwarders, couriers and different climatic zones.

The risks associated with failure to adequately assess the competence of the Contract Acceptor could be highly significant and result in regulatory action and/or patient distress and/or commercial loss.

Implementation
There are four key steps in initially assessing the competence of a potential Contract Acceptor:

1. Selection based on commercial aspects, such as cost and stated capabilities;
2. Audit to the applicable GDP standards and any specific technical standards, KPIs or other requirements;
3. Obtaining commitment to each element of the Contract or adjusting it to suit each party;
4. Confirming the personnel responsible for each role defined within the Contract, their contact details (and those of their deputies), the communication required for each activity, and the updating process.

Maintaining the approved status of the contractor can be achieved by monitoring, reassessment, and periodic auditing. For example:

- Records from data loggers should be monitored and evaluated for each delivery;
- Periodic assessment of the Contract Acceptor's performance in respect of KPIs and complaints should be performed. Typically, this should be done annually;
- Audits should be performed relatively frequently initially, e.g., at least annually, reducing to a lower frequency once confidence is established and justified. The scope of audits should be based on current (and potential future) outsourced activities, which may be a sub-set of the full services offered by the contractor. During the audit, particular attention should be paid to the level of non-conformances and the effectiveness of the CAPA system as these may provide valuable insight of the overall level of GDP compliance at the site. Recent regulatory performance is also important in assessing potential risks arising from the use of the contractor.

Where there has been a change to the scope of the contracted activities, a formal review in the form of an audit should be carried out to ensure that the contracted party remains suitable to carry out the contracted activity.

The Contract should specify that the Contract Giver can perform an inspection of the Contract Acceptor's site at any time with an appropriate notice period and that if required a representative of a Regulatory Authority can enter the premises of the Contract Acceptor for the purpose of auditing in relation to GDP activities carried out on behalf of the Contract Giver.

Note that auditing is only one part of ensuring the ongoing performance of the Contract Acceptor. Agreement on performance indicators and good regular communication between parties is also needed.

7.2 Contract Giver

The Contract Giver should provide the Contract Acceptor with all the information necessary to carry out the contracted operations in accordance with the specific product requirements and any other relevant requirements.

What is the rationale for this point of guidance?
It is implicit that without such information the Contract Acceptor will not be able to fulfil their responsibilities correctly.

What are the benefits and risks associated with this point of guidance?
The benefit is that provision of such information will help minimize mistakes and adverse consequences. The risk associated with failure to do this are an extremely high probability that problems will occur.

Implementation
The Contract Giver should provide all the information that the Contract Acceptor requires in order to comply with the quality and technical requirements of the Contract. Examples are:

- Storage requirements for each climatic zone;
- Anticipated delivery volumes over the course of a year, recognizing that many products are used seasonally and that this could exceed the Contract Acceptor's capacity to store them;
- Recognising this potential storage problem, approved (by the Contract Giver) back up bulk storage facilities where necessary, to accommodate seasonal peaks in delivery volumes;
- Maximum tolerances for permitted time outside defined storage conditions;
- For each country involved, the specification (and validation records) for the controlled temperature transit container which has been validated for deliveries by couriers who can only store at ambient temperature;
- Records of such validation;
- Clarity on how the release of batches to each particular market will be authorized and by whom, in order to comply with national regulations.

A joint review should occur to ensure that both parties are satisfied with the information provided.

The Contract template in Appendix 1 provides a number of points to consider that will facilitate this information exchange.

The Contract Giver and Contract Acceptor should ensure that the Contract includes appropriate confidentiality clauses that enable full disclosure of information required by the Contract Acceptor, e.g., product safety datasheet so that accidental spillages can be managed.

Where new information becomes available, the Contract should be updated.

7.3. Contract acceptor

The Contract Acceptor should have adequate premises and equipment, procedures, knowledge and experience, and competent personnel to carry out the work ordered by the Contract Giver.

What is the rationale for this point of guidance?
To safeguard the product and ensure compliance with GDP.

What are the benefits and risks associated with this point of guidance?
The benefit is robust assurance that the product will be effective and safe when used.

Implementation
This is implemented by complying with the requirements of GDP and meeting each of the additional specific requirements in the Contract.

Although it is primarily the responsibility of the Contract Giver to ensure that the Contract Acceptor is suitable, the Contract Acceptor should identify any challenges they might face and advise the Contract Giver **before** accepting work. For example, if they do not have sufficient capacity within the defined storage facility for the anticipated volume of work over a full year.

7.3. Contract acceptor

The Contract Acceptor should not pass to a third party any of the work entrusted to him under the contract without the Contract Giver's prior evaluation and approval of the arrangements and an audit of the third party by the contract giver or the Contract Acceptor. Arrangements made between the Contract Acceptor and any third party should ensure that the wholesale distribution information is made available in the same way as between the original contract giver and Contract Acceptor.

What is the rationale for this point of guidance?
To ensure that where sub-contracting takes place it occurs in a controlled manner.
To ensure that the Contract Giver maintains full knowledge of the supply chain and is in a position to evaluate any changes and assess their impact.

To ensure that where a Contract Acceptor sub-contracts work to another third party that the arrangements agreed with the Contract Giver are fully maintained.

What are the benefits and risks associated with this point of guidance?
The risks with further sub-contracting are that standards may be at variance with those agreed between the initial contracting parties.

Implementation
The Contract Acceptor should have a process to manage sub-contracting which should involve prior approval by the Contract Giver **before** implementation.

Approved sub-contractors should be defined in the Contract and any intended changes notified to the Contract Giver. However, the Contract Giver should specify in the Contract when they would wish to audit and/or approve sub-contractors prior to use.

7.3. Contract acceptor

The Contract Acceptor should refrain from any activity which may adversely affect the quality of the product(s) handled for the Contract Giver.

What is the rationale for this point of guidance?
To ensure that product quality is not adversely affected in the supply chain.

What are the benefits and risks associated with this point of guidance?
The Benefits are implicit in the rationale i.e., it will minimise the commercial liability to the business and/or key personnel.

Examples of risks and potential consequences could include:
- Poor handling leading to physical damage to product packs;
- Storing medicinal products close to materials that could taint the product;
- Storage outside the specified storage conditions which can lead to chemical or physical degradation. e.g. sterile vials damaged by freezing.

Implementation
This requirement can be met by:
- Complying with general GDP requirements;
- Complying with any product specific and technical requirements detailed in the Contract;
- Taking account of any additional information provided by the Contract Giver;
- Being aware of limitations in knowledge and if in doubt asking the Contract Giver for advice.

7.3. Contract Acceptor

The Contract Acceptor must forward any information that can influence the quality of the product(s) to the Contract Giver in accordance with the requirement of the contract.

What is the rationale for this point of guidance?
To ensure that product quality is maintained throughout the supply chain. The Contract Giver will either be the Marketing Authorisation Holder (MAH) or knows how to contact the MAH. The MAH is best able to determine potential impact and can take appropriate action or provide advice.

What are the benefits and risks associated with this point of guidance?

Benefits
It provides the Contract Acceptor with both an understanding of why they should contact the Contract Giver in these circumstances and the expectations of what they will receive in return.

Risks
In the absence of this type of dialogue, potential problems may go unreported and product quality may be jeopardised. A risk is that they do not either have the confidence to do so or do nothing for fear of upsetting the Contract Giver.

Implementation
- Establish and maintain regular and effective communication with the Contract Giver. Regular face-to-face meetings are the best method, especially initially, but once a relationship has been established, Skype, teleconferences or equivalents can be effective occasional alternatives.
- Continue to be very open with the Contract Giver; not hiding any failures in compliance in respect of either GDP or the Contract.

Note:
- Any such failure to be open will probably be detected at a later stage and adversely impact future business relationships.
- Where the Contract Giver does not have the expertise to assess the information provided, they should forward the information and seek advice as appropriate. For example, if a third party logistics provider is a Contract Acceptor to a wholesaler (Contract Giver) and the information relates to a temperature excursion during transportation, they will probably need to arrange to share the information with the MAH and seek their advice as to whether the product remains suitable for use.
- Ensure that there is a procedure describing what actions to take and providing a link to the correct contacts.

Chapter 8 – Self-inspection

8.1. Principle

Self-inspections should be conducted in order to monitor implementation and compliance with GDP principles and to propose necessary corrective and preventive actions (CAPAs).

What is the rationale for this point of guidance?

A well-managed self-inspection programme can provide a much better insight into the performance of an organisation's level of GDP than a time-limited third party, statutory regulatory GDP or voluntary ISO 9001 audit. The GDP Guideline contains very similar requirements to the GMP Guideline. There is a difference in terminology between GMP/ GDP self-inspections and ISO 9001 internal audits, but the principles are the same.

Self-inspections reinforce the importance of company staff and management taking responsibility for quality. They:

- Check compliance with GDP requirements, helping to prepare for customer and regulatory audits;
- Increase management awareness and staff awareness of potential risks;
- Provide input to facilitate continuous improvement.

What are the benefits and risks associated with this point of guidance?

Benefits

- The confidentially of the process enables both internal auditors and auditees to be more open regarding the state of compliance with GDP. Note: see later for level of confidentiality permitted;
- Internal people understand the system better and are therefore in a better position to identify any potential risks and opportunities for improvement;
- The frequency of the programme can be tailored to the level of risk in real time to enable an effective management response, if required;
- Senior management and the Responsible Person (RP) can respond to both:
  - High levels of GDP by positive recognition which can be highly motivating for staff
  - Potential risks to the business, customers and end-users in time to initiate CAPA before any damage is done;
- Benefits for internal staff involved in conducting or assisting the self-inspection are:
  - Increased knowledge of GDP and why it matters;
  - The opportunity to learn more about the quality system and wider business;
- An active, risk based assessment with effective CAPA can provide confidence to customers of the organisation's ability to avoid potential risks, which may compromise their business;
- The organisation's GDP WDA licence is less likely to be rescinded by national regulators, as a consequence of critical GDP failings being detected either during inspection or 'in the marketplace'.

Risks

- If the organisation doesn't treat this requirement as business critical then its ability to avoid potential risks is compromised. As a business critical requirement, self-inspection requires:
  - Sufficient trained personnel to manage and operate the system;
  - Minimal delays in completing, agreeing and/or publishing the findings;
  - Commitment to thorough and timely completion of the programme and/or incomplete coverage of the system;
  - Low/non-existent/delayed management involvement in review of the findings and CAPA.

Implementation

The implementation process is described in the following section.
A useful reference is the Guidelines for auditing management systems (ISO 19011:2011)

8.2. Self-inspections

A self-inspection programme should be implemented covering all aspects of GDP and compliance with the regulations, guidelines and procedures within a defined time frame. Self-inspections may be divided into several individual self-inspections of limited scope.

Self-inspections should be conducted in an impartial and detailed way by designated competent company personnel. Audits by independent external experts may also be useful but may not be used as a substitute for self-inspection.

All self-inspections should be recorded. Reports should contain all the observations made during the inspection. A copy of the report should be provided to the management and other relevant persons. In the event that irregularities and/or deficiencies are observed, their cause should be determined and the corrective and preventive actions (CAPA) should be documented and followed up.

What is the rationale for this point of guidance?

Self-inspection programme:

- Full coverage with appropriate prioritisation based on risk assessment is consistent with supporting both compliance and business performance;
- Defining the time frame for the whole programme is very important to ensure that a balance is maintained and all operational activities are inspected reasonably frequently based on evidence of compliance;
- Provides a basis for assessment and management of resources – for auditors and auditees.

Independence:

- Provides greater objectivity around assessments than would be the case if inspecting work for which the auditors have operational responsibility.

External experts:

- Will usually have seen many different organisations and together with their fresh pair of eyes and experience can occasionally identify non-compliant practices which have been overlooked.

Records:

- Are essential for accurately communicating findings to internal management and staff;
- Provide evidence, which can be used to make decisions and initiate action;
- Provide confidence to customers and regulators that a robust quality system is in place.

Note: In order to encourage full and open reporting from self-inspections, customers and regulators will not, typically expect to be shown the content of internal audit reports but will look for documented evidence that a system is in place and effective with:

- Self-inspections being carried out according to the schedule set;
- Reports being produced in a timely manner;
- CAPAs being raised to address findings;
- CAPAs being completed with no excessive, unexplained or unjustified delays.

What are the benefits and risks associated with this point of guidance?

Benefits

- If done well, the organisation will know its level of compliance with GDP and risks to the business and will be able to make appropriate decisions to address any gaps before serious issues arise;
- Customers are more likely to continue to use the services of the distributor because of confidence in a sustained high level of compliance and good customer service arising from the wider quality system.

Risks

If there is not a good self-inspection programme in place, then there are risks of:

- Lack of RP/management awareness of GDP compliance status;
- Impact on delivery of safe and secure medicines to customers with subsequent potential damage to the commercial success of the business;
- Regulatory censure with potential for loss of licence.

Implementation

The process flow in Figure 5 and the notes in Table I are based on the ISO 19011:2011 guidelines.

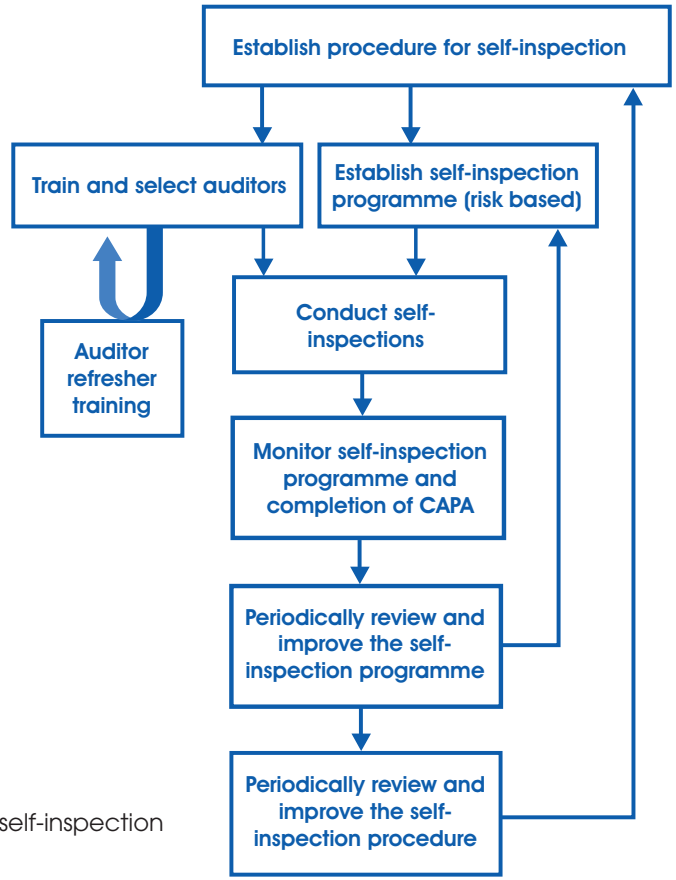

Figure 5: The self-inspection process cycle

Table I: Elements of a self-inspection process and additional guidance notes

SOP	• Describes how to do all these elements in company • Clear on responsibilities both for auditors and management See template as example of content

Audit programme (ISO 19011, Section 5)	Risk-based approach used to determine what areas to cover with what frequency:
	• All relevant areas of GDP should be covered at least every 2-3 years and all high risk activities at least annually;
	• Use internal quality metrics to help assess criticality:
	  • Previous self-inspection findings;
	  • Customer audit findings;
	  • Deviations, Complaints;
	• Pay particular attention to recent changes and information:
	  • Have recent regulatory requirements and/or commitments been implemented?
	  • Have business (procedural) changes been implemented effectively?
	  • Staff or responsibility changes can increase risk and should be checked;
	  • Review reports published by national regulatory agencies either online or at symposia analysing the areas where they have found major issues.
	
	• The risk assessment process used will probably identify certain activities, contractors and locations require more frequent self-inspection. Examples might be:
	  • Outsourced cold chain;
	  • New or infrequently used contractors such as couriers;
	  • New or distant depots which are expensive to visit;
	  • Intermediate freight forwarders who may not be aware of GDP.
	
	The programme should be reviewed and approved by the RP.
	
	Although a programme will typically be prepared to cover a year in advance, it should be subject to review and revision in real time, when a significant change occurs.
	
	In addition to review and revision in response to significant changes, the programme should be subject to ongoing monitoring to ensure its effective implementation. Factors to consider include:
	• Conformity with audit programmes, schedules and audit objectives;
	• The performance of the auditors;
	• Resources to complete the audit plan;
	• Any feedback from management, auditees, auditors or regulators.
	
	At the end of each audit cycle, a review should be conducted and lessons learnt incorporated as improvements in the following programme.

Auditor selection and training (ISO 19011, Section 7)	• Current GDP knowledge, including any national-specific guidelines noting that there are some variations; • Technical knowledge on matters such as calibration of instruments; • Trained in practical auditing; • Demonstrated competency in ability to put training into practice. • It is recommended that the RP actively carries out a significant proportion of the self-inspections; • If external experts are engaged to perform additional audits, then the RP should typically accompany them and play an active role in the audit.
For specific audits (ISO 19011, Section 6)	
Select auditor(s)	• In addition to the general auditor selection and training considerations (above), it should be ensured that the auditors are independent of the activities being audited.
Plan audit (ISO 19011, Section 6.3.2)	• Covers defined scope from audit programme; • Agreed with internal management and communicated to those impacted; • Creation of a checklist can provide a useful prompt for an auditor
Conduct audit	• Collect evidence of both compliance and non-compliance with GDP, together with opportunities for business risk reduction; • Be friendly, listen well and respond empathetically to auditees; • Ensure that no personal ideas, opinions or emotions are expressed; • Communicate to the auditee throughout the audit when any non-conformances are observed and agree confirmed non-conformances and any recommendations with him/her. Ensure that no surprises (new topics) are raised during the closing meeting; • At the closing meeting, communicate the general level of conformance and each significant non-conformances to the assembled auditees and management.
Report	• Set a standard for issuing a report as promptness helps to underline the importance of inspections and enables prompt CAPA. A typical target is 7 days; • Include a clear scope statement – what was and was not covered; • Should include evidence of what was looked at and the outcome of review – compliance or finding(s) requiring CAPA; • Should reflect what was communicated at the closing meeting (the report can be used to provide more detail, but should not bring up new issues); • Findings may be categorised according to criticality (see SOP template for example) to aid prioritisation.

Management review	• The typical frequency of organisations operating a 'tick box' approach to management review is to hold them annually. A much more effective frequency is a baseline of 3 monthly for a review of trends with any high risk non-conformance being flagged up immediately. See Chapter 1; • In each case findings should be reviewed, CAPA agreed with resources assigned, targets set for implementation by the manager responsible.
Close out (CAPA and follow up)	• Define in the company SOP the responsibilities of both auditors and line management for CAPA creation and/or close out. It is recommended that the auditor is involved at least to the point of CAPA approval as the background information they have from the inspection can be used to assess the suitability of the CAPA to address non-conformances identified; • RP to approve CAPA. See GDP Guideline Chapter 1.

An outline SOP template and self-inspection checklists are available through the PQG Shop/ECA website as resources, but it is stressed that these should be customised to reflect the specifics of the company or audit scope.

National Competent Authority and EudraGMDP websites can be useful for highlighting the kind of issues that regulatory agencies are finding and citing in non-compliance reports. If these elements are factored into planning at both the programme and specific audit stages, it can be assured that any issues are identified and CAPA implemented through the self-inspection process, thus preventing deficiencies arising from regulatory agency inspections.

Chapter 9 – Transportation

9.1. Principle

It is the responsibility of the supplying wholesale distributor to protect medicinal products against breakage, adulteration and theft and to ensure that temperature conditions are maintained within acceptable limits during transport.

Regardless of the mode of transport, it should be possible to demonstrate that the medicines have not been exposed to conditions that may compromise their quality and integrity. A risk-based approach should be utilised when planning transportation.

What is the rationale for this point of guidance?

Despite normally good intentions on the part of licensed suppliers, the controls necessary to ensure that medicinal products are distributed in a manner which avoids; damage, adulteration, theft or deterioration, due to adverse temperature conditions, are not always maintained adequately. The specific controls needed are detailed within the guidance document.

What are the benefits and risks associated with this point of guidance?

Benefits

Ensures that only medicinal product that are fit for purpose are supplied to patients.

Falsification of medicines is an increasing issue on the worldwide pharmaceutical market and results in sub-standard products being taken by patients across the world, creating a risk to public health. Everyone involved in the pharmaceutical supply chain has a responsibility to ensure only genuine products make it to patient level, having a robust and secure supply chain is one way of ensuring this.

Risks

Not having a secure, risk-assessed supply chain can result in sub-standard products being supplied to patients. If a product has particular storage requirements such as +2°C to +8°C, these conditions should be maintained so the product continues to meet the requirements of its licence. Temperatures outside of this range will affect the efficacy of the product.

Implementation

The supply chain should have adequate security to prevent theft of product and minimise the risk of falsified products entering the supply chain. The chosen

route of transportation should ensure that the products are maintained within their required temperature parameters at all times. Documented evidence should be kept and be available, showing the supply chain route that the products were distributed through and the conditions to which they were exposed during transportation. This should be demonstrated with temperature monitoring in vehicles via data loggers included in the shipment or by previous qualification of the transportation route (taking into account seasonal variations). All distribution of medicinal products should be based on a risk assessment and documented accordingly taking into account the various factors detailed in 9.2 which could affect the products.

Further detailed guidance is provided in subsequent clauses.

9.2 Transportation – Editors notes
This section is large and covers a number of different aspects so, for clarity, it has been broken down into different sub-sections for treatment in this guidance document.

The Commission Guideline does not sub-number the paragraphs in this section, but, for ease of reference, these have been added to this document using square brackets together with an indication of aspects covered. The same annotation is used in Appendix 2.

9.2. Transportation ((i)- Understanding and control of required storage conditions)

The required storage conditions for medicinal products should be maintained during transportation within the defined limits as described by the manufacturers or on the outer packaging.

If a deviation such as temperature excursion or product damage has occurred during transportation, this should be reported to the distributor and recipient of the affected medicinal products. A procedure should also be in place for investigating and handling temperature excursions.

What is the rationale for this point of guidance?
Product storage conditions are determined through stability testing and agreed with regulatory agencies. Deviation from these storage conditions puts the quality of products at risk. Unless temperature excursions and incidents of product damage are flagged to the supplier patient safety could be impacted.

What are the benefits and risks associated with this point of guidance?

Benefits
- Ongoing assurance of the quality of the distributed product;
- Facilitation of investigations of temperature excursions or incidents resulting in product damage during transportation, which may require reference to the MAH and leading to appropriate CAPAs.

Risks
Without investigation of deviations, not only is there a risk of reduced quality product being supplied to patients but also an ongoing risk of subsequent shipments being impacted in the same way. Serious adverse contractual, financial or legal implications could result from the supply of impacted product.

Implementation
- Know the products being supplied, e.g.:
  - What are the storage requirements?
  - Does the manufacturer make any further recommendations?
  - What quantity is being shipped?
- Know the Supply Chain, e.g.:
  - What is the distance of the journey?
  - What routes are to be taken?
  - Which modes of transport are required?
  - What is expected journey time?
  - What are expected conditions (e.g., Scandinavia in January or South of France in July);
  - Are there any points in the supply chain where delays can be anticipated, e.g. countries with a history of customs delays?
- Outer packaging and transportation should be selected on the basis of their ability to maintain the required storage conditions for the products shipped (see Sections 9.3 and 9.4);
- Distributors should ensure that shipping containers and/or the accompanying documentation clearly indicates the required storage conditions.
- The required conditions should be specified when booking transportation and planning delivery routes;
- The IATA label is recommended for time and temperature sensitive products.
- Required storage conditions and any permitted temperature excursion parameters (temperatures and times) should be specified in the Contract/Technical Agreement, which should also include a list of contacts to enable prompt action to be taken in the event that these are exceeded;
- Customers should be encouraged to report any issues identified on receipt and these complaints should be dealt with as detailed in Section 6.2;
- Temperature excursions (including extent and duration) should be notified immediately (as per Contract/Technical Agreement terms);

- A detailed procedure should be in place for investigating, handling and managing all temperature excursions including during transportation. This should include reference to the Responsible Person or the Wholesaler or Qualified Person in the MAH or the recipient of the affected medicinal product in a timely fashion and recorded;
- Decisions made by the distributor and recipient should be recorded and followed.

9.2. Transportation ((ii) Control of vehicles)

It is the responsibility of the wholesale distributor to ensure that vehicles and equipment used to distribute, store or handle medicinal products are suitable for their use and appropriately equipped to prevent exposure of the products to conditions that could affect their quality and packaging integrity.

There should be written procedures in place for the operation and maintenance of all vehicles and equipment involved in the distribution process, including cleaning and safety precautions.

Risk assessment of delivery routes should be used to determine where temperature controls are required. Equipment used for temperature monitoring during transport within vehicles and/or containers should be maintained and calibrated at regular intervals at least once a year.

What is the rationale for this point of guidance?

To make clear where the responsibility lies and to specify in the procedures the actions required to maintain vehicles and equipment and to ensure that appropriate controls are applied. An objective risk assessment of delivery routes should enable selection of appropriate storage containers, and the specification of controls for each stage of the supply chain. Regular calibration of temperature monitoring devices will provide confidence in the data obtained.

What are the benefits and risks associated with this point of guidance?

As per rationale and earlier benefits/risks. If temperature monitoring equipment isn't calibrated and accurate at all times, then product is at risk due to potential erroneous readings.

Implementation

- Wholesalers/manufacturers should map out their whole supply chain and know what controls are in place for temperature, humidity, security and risk of cross contamination at each stage of transportation. This should include the use of all temporary storage locations, hubs, etc. All locations should be approved and audited against specific storage/ transportation standards and requirements. See also section 9.2 (v);
- The type of product (e.g. cold chain, narcotics) should be carefully considered to ensure storage and security in the transportation process;
- Procedures need to be in place to ensure the appropriate maintenance and use of all vehicles and equipment, including monitoring equipment, involved in the distribution process;
- Delivery routes should be assessed to identify the hazards associated with intended transport method and to understand the storage and climatic conditions for each specific stage of the supply chain. These should then be mitigated as far as practicable to minimise the probability of issues occurring.

9.2. Transportation ((iii) Dedicated vehicles)

Dedicated vehicles and equipment should be used, where possible, when handling medicinal products. Where non-dedicated vehicles and equipment are used, procedures should be in place to ensure that the quality of the medicinal product will not be compromised.

What is the rationale for this point of guidance?

A dedicated vehicle is one which is used to transport medicinal products only. This practice automatically reduces certain risks, e.g., potential contamination with spillages of toxic chemicals or adsorption of strong odours from other products, such as spices.

Typically, the dedication goes further with customised vehicles (see Implementation) carrying only one customer/supplier's product or consignment and travelling from an authorised site to the approved final delivery point under procedural control. This provides a very high level of control and security.

What are the benefits and risks associated with this point of guidance?

Benefits

Dedicated vehicles reduce the risk of cross-contamination and are more likely to provide a safe, secure and traceable method of transporting medicinal product within a controlled delivery process.

Risks

If non-dedicated vehicles are used for medicinal products they could be stored alongside other types of product, e.g., agricultural fertilizers, chemicals, food, flowers etc., with risk of cross-contamination. Non-dedicated vehicles may also be associated with lack of appropriate controls risking adverse conditions or security incidents.

Implementation

Use of dedicated transportation and equipment and trained drivers from

approved transport companies, to store, handle and distribute products using approved transport companies and trained drivers should ensure safe, secure and timely delivery of products. The suitability of packaging, materials should be tested to ensure no breakage or damage in normal transportation modes.

All transportation companies under the terms and conditions of contract (see Chapter 7) should be approved and, ideally, audited to ensure that appropriate procedures are in place for maintenance, calibration, cleaning and safety of equipment used in the distribution process.

All approved transport companies used should be listed on an Approved Vendor/Supplier Master List.

Dedicated vehicles

- Specify the vehicle to maximise security and assurance of product quality:
  - Solid side construction;
  - Air ride suspension;
  - Rear opening doors which are locked/sealed;
  - GPS tracking;
  - Qualified temperature control equipment;
  - Calibrated temperature monitoring equipment;
- Ensure regular cleaning and maintenance, including annual re-calibration of temperature monitoring equipment, with records being kept;
- Ensure drivers have GDP training so that they know the criticality of following instructions;
- Ensure breakdown coverage;
- If using a vehicle provided by a third party, ensure a Contract/Technical Agreement is in place specifying these requirements.

Non-dedicated vehicles

- Ensure that any sharing is risk assessed and managed (procedure in place as per guideline);
- Apply as many of the recommendations for dedicated vehicles as possible to maximise security and assurance of product quality;
- Drivers should be aware they are carrying medicinal products and of the particular importance of safeguarding these. They should know the risks associated with the other materials carried.

9.2. Transportation ((iv) Deliveries and emergencies)

Deliveries should be made to the address stated on the delivery note and into the care or the premises of the consignee. Medicinal products should not be left on alternative premises.

For emergency deliveries outside normal business hours, persons should be designated and written procedures should be available.

What is the rationale for this point of guidance?

Ensuring delivery to the intended recipient (consignee) ensures continuity of 'chain of custody' reducing the risk of entry of falsified products into the supply chain and helping to ensure continuous storage under the correct conditions to assure product quality.

What are the benefits and risks associated with this point of guidance?

Benefits

- Products are at all times in the possession of trained personnel, assuring their security
- The final consignee is able to deal appropriately with the receipt; checking product integrity, stopping temperature monitors/recording temperature parameters as required, and transferring to appropriate storage on their premises.
- Ensures patients always receive their medication in an emergency situation.

Risks

In the absence of specific arrangements for emergency 'out of hours' deliveries, it is likely that an appropriate individual will not be available to receive the shipment increasing the risk of product being left inappropriately:

- Products left unattended may be lost and Proof of Delivery (POD) may not be available;
- Products delivered to an alternative consignee may be stored incorrectly;
- Products delivered to alternative premises may be misused;
- Patients may not receive their medication in a timely manner.

Implementation

- Ensure that any specialist carriers that may be required for emergency 'out of hours' deliveries are identified and that contracts are put in place in advance of their use being needed;
- Prepare an SOP for the deliveries outside of normal business hours, which includes the following:
  - The provision of a 24/7 service via the normal operations telephone numbers and e-mail;
  - Details of the names and mobile numbers of the persons responsible for delivering and receiving 'out of hours' medicines for all deliveries;
  - Use of appropriately GDP trained drivers only;
  - Provision of online/GPS 24/7 tracking where appropriate;
  - Details of contingency plans are defined, for example; "truck/transport by road if a flight is cancelled and no further flights are available";

- Ensure that the delivery notes should include, as a minimum:
  - The full delivery address (including consignee name and telephone number);
  - Description and quantity of the product(s);
  - Shipping and storage conditions for the product(s).
- Other Delivery note details might also include carrier details; airway bill, etc.
- Specify a 'hand-to-hand' service for the specific consignee indicated on the delivery note with explicit prohibition of deliveries being left at alternative premises unless it was agreed and approved in advance with the supplier (manufacturer, wholesaler, etc.) and the receiving site;
- In some instances, ensure that, a specific time slot for receiving the delivery is agreed up-front with the receiving site and should be adhered to by the carrier;
- Ensure that carriers have procedures in place, detailing the actions to be taken in the event that the designated consignee is not available or there is any other reason why that delivery cannot be made as specified. e.g., if the designated consignee is unavailable on arrival, or there are delays in transit (which should be notified to the receiving site as soon as possible);
- Define in the contract that, for 'next day' deliveries, the carrier should normally attempt to deliver medical products before 12:00 on the specified date;
- Account for the delivery of all shipments. Proof of delivery (POD) should be available for each shipment with the date and time of delivery and the name and signature of the recipient, documented at the time of delivery. This is usually retained by the carrier.

9.2. Transportation ((v) Contractors and temporary storage)

Where transportation is performed by a third party, the contract in place should encompass the requirements of Chapter 7. Transportation providers should be made aware by the wholesale distributor of the relevant transport conditions applicable to the consignment. Where the transportation route includes unloading and reloading or transit storage at a transportation hub, particular attention should be paid to temperature monitoring, cleanliness and the security of any intermediate storage facilities.

Provision should be made to minimise the duration of temporary storage while awaiting the next stage of the transportation route.

What is the rationale for this point of guidance?

- To ensure that a contract is in place making clear responsibilities and requirements of each party in the supply chain;
- To minimise at all stages in the supply chain the risk to products arising from inappropriate storage.

Figure 6: Key points to consider for your procedure on 'Managing Third Party Transportation Contractors'

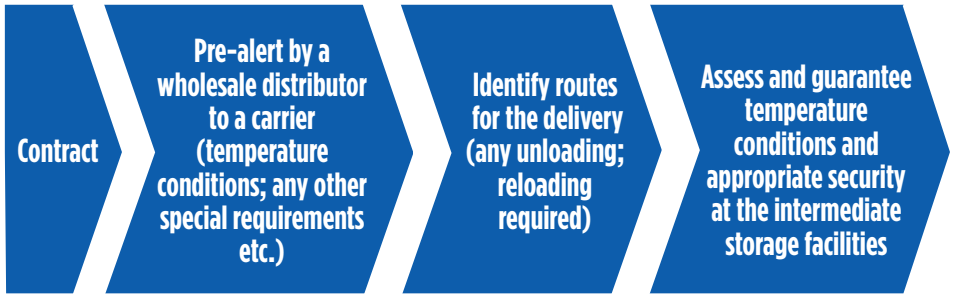

Figure 7: Key factors to include in your contract with Third Party Transportation Contractors.

What are the benefits and risks associated with this point of guidance?

Benefits

- Clear and effective communication within the contract will avoid misunderstandings between parties;
- A focus on higher risk areas in the supply chain will enable assurance of appropriate arrangements being in place.

Risks

- Misunderstandings result in inappropriate storage/handling impacting product quality and/or security

Implementation

- Follow the guidance in Chapter 7 and ensure that all requirements are clearly specified in a contract;
- In particular, ensure that limitations on storage outside controlled/licensed facilities are specified;
  Note: Guidance on the maximum time that temporary storage facilities may be used and whether they are required to be licensed is not harmonised across Europe/globally. It is therefore important that companies are aware of any local expectations;
- Define and confirm the required mode of transportation and relevant transport conditions at the time of scheduling;
  Note: this is usually via web based systems or telephone/e-mail communication.
- Ensure that transportation providers have clear procedures for the temperature and environment monitoring required for each storage/transport method and location. Include the possibility of:
  - transfer of customs/flight delayed shipments to an appropriate controlled storage facility (this might be an airline facility at the airport involved);
  - repacking into a freshly conditioned validated packaging with replenishment of dry ice;
  - use of a refrigerated vehicle;
- The "Risk assessment of delivery routes" mentioned earlier should identify risks and enable mitigation actions to be taken. e.g. predetermination of routes with further evaluation to determine the distance and time between loading point and collection; likely duration in customs; security risks at each point in the supply chain, etc;
- Arrange an audit for any high risk temporary locations;
- Ensure that all shipment documents (e.g. licenses; import certificates; other local authorisations) are up-to-date in order to minimise the risk of additional unloading, temporary storage and reloading by customs authorities;
- Never underestimate the potential for delays by Customs officials;
- Carefully plan and use Third Party Logistics (3PL) partners that have the expertise and trained staff to manage your supply chain successfully. It is imperative that they can be relied on to inform you immediately of any unplanned events with the delivery;
- Maximise the use of pre-clearance of shipments and do not make shipments, especially of temperature sensitive products, until approvals are received;
- It is very important that determined efforts are made to establish effective and reliable communication channels and shared understanding between all parties in the supply chain;
- Temporary storage should be subject to a level of control, aligned with the known stability profile of the product;
- Where possible, use licenced sites that have successfully passed regulatory inspections for temporary storage. These sites will ensure, under their Quality Management System, a safe, clean, secure and temperature compliant facility, supported by compliant documentation systems;
- Transit delays leading to temporary storage should be addressed as a matter of urgency and utilise the next available flight or alternative transport.

9.3. Containers, packaging and labelling

Medicinal products should be transported in containers that have no adverse effect on the quality of the products, and that offer adequate protection from external influences, including contamination.

Selection of a container and packaging should be based on the storage and transportation requirements of the medicinal products; the space required for the amount of medicines; the anticipated external temperature extremes; the estimated maximum time for transportation including transit storage at customs; the qualification status of the packaging and the validation status of the shipping containers.

Containers should bear labels providing sufficient information on handling and storage requirements and precautions to ensure that the products are properly handled and secured at all times. The containers should enable identification of the contents of the containers and the source.

What is the rationale for this point of guidance?

- To ensure that medicinal products are not adversely affected by the containers used to ship them, or other environmental factors.
- To prompt appropriate selection of containers and packaging for each shipment.
- To ensure application labels are sufficiently detailed to clearly identify contents, source and destination, to help ensure proper handling and storage of the product throughout its distribution.

What are the benefits and risks associated with this point of guidance?

Benefits

- Selecting and using the correct shipping container and/or packaging and applying the appropriate labels will ensure that medicinal products are received at the intended destination fit for use.
- When external shipping conditions are well understood and packaging solutions of known reliability are used, there will be greater confidence in the shipments.

Risks

- Without assessing the appropriate shipping container or packaging for a product, it is likely that the product will be subjected to temperature conditions that could adversely impact the efficacy of the product;
- Without labelling to identify the required shipping and handling conditions, the wrong transportation method could easily be used in error, even if the supplier has assessed what the appropriate method of transportation should be.

Implementation

- Be aware of any packaging required or recommended by the MAH to help maintain the defined storage conditions;
- Assess the suitability of validated packages provided by the packaging or logistics provider, and use these wherever possible;
- Select shipping containers based on the product; storage/transportation conditions, quantity to be shipped and shipping route (air, road, or sea). For example:
  - A relatively small quantity of a high value cold chain product to be shipped to Greece would be best placed in either an active temperature controlled container, or a validated insulated box (shipper). Noting that if the latter method is used dry ice/cool packs may need to be replenished during the transit;
  - A 26-pallet shipment of +15°C to +25°C product being shipped from a manufacturing plant in India to the UK, would be best shipped in a temperature controlled reefer;
- Consider whether the whole shipment is for delivery to a single location, or whether multiple drops will be made en-route. The risk associated with multiple drops is much higher and will require more extensive qualification;
- Perform a specific risk assessment, taking account of 'worst case' scenarios. e.g. in terms of, for example seasonality and document the justification and evidence for the packaging system selected;
- Use Section 9.2(i) guidance to risk assess delivery routes and select containers that will provide the required buffer between the likely extremes of temperature and humidity and the product, so that the product remains within the defined storage conditions;
- Qualify the shipping route and method by conducting shipping studies, which includes:
  - Investigation of temperatures achieved on the outside of packages shipped to the chosen destinations;
  - Several 'dummy' shipments to selected destinations, covering seasonal extremes at both ends of the supply chain;
  - Studies which anticipate any potential issues during transit can take a lot of the guess work out of the assessment of the temperatures or humidity to which products might be exposed;
  - Assessment of the damage sustained by re-usable packaging in order to determine a maximum permitted number of cycles, to be referenced in procedures. Consider also cost feasibility;
- Use the data from both dummy and actual shipments to build a performance database of:
  - Temperature results (internal vs. external where possible);
  - Transit times;
  - 3PL/Freight Forwarders;
  - Notable events/failures/trends during transit.

To maximise the value from this, the data should be updated continually and reviewed periodically at a frequency indicated by the variations observed.

- Use the shipping studies:
  - to identify possible risk areas, e.g., locations where delays or temperature excursions are more likely;
  - for investigative purposes, if problems arise with an existing packaging and/or shipment lane;
- Shipping studies can also be useful for investigative purposes if problems arise with an existing packaging and/or shipment lane;
- Select freight-forwarders and/or logistics companies with care and support them well - they are an important partner in implementing this process and improving the efficiency of capturing data;
- Ensure that all shipments of medicinal products bear labels showing the type of product, the required temperature conditions and any special handling requirements. Labelling of a shipment should be clear and visible and the use of diagrams wherever possible, particularly when shipping across borders. The IATA label is recommended for time and temperature sensitive products;
- Ensure that procedures require that the container being used should be checked before loading for:
  - any signs of damage which might affect the temperature control of a vehicle or reefer;
  - any signs of debris or potential contaminants left by previous shipments such as chemicals.

9.4 Products requiring special conditions – Editors notes
This section is large and covers a number of different aspects so, for clarity, it has been broken down into different sub-sections for treatment in this guidance document.

The Commission Guideline does not sub-number the paragraphs in this section, but, for ease of reference, these have been added to this document using square brackets together with an indication of aspects covered. The same annotation is used in Appendix 2.

9.4. Products requiring special conditions ((i) Safety of narcotics, highly active and radioactive materials)

In relation to deliveries containing medicinal products requiring special conditions such as narcotics or psychotropic substances, the wholesale distributor should maintain a safe and secure supply chain for these products in accordance with requirements laid down by the Member States concerned. There should be additional control systems in place for delivery of these products. There should be a protocol to address the occurrence of any theft.

Medicinal products comprising highly active and radioactive materials should be transported in safe, dedicated and secure containers and vehicles. The relevant safety measures should be in accordance with international agreements and national legislation.

What is the rationale for this point of guidance?
Distribution of certain products such as narcotics, radioactive or psychotropic substances should be carried out in accordance with procedures that will ensure national and international legislative requirements are met.

What are the benefits and risks associated with this point of guidance?

Benefits
By having good procedures and well trained competent staff, regulatory requirements will be met and the risk of theft is minimised, avoiding insurance penalties and loss of customer confidence.

Risks
The value of these products is high and criminals will exploit any and every weakness in control and security.

Implementation
- Understand the legal requirements and specify responsibilities;
- Ensure compliance with these requirements in both procedures and contracts with third parties;
- Specify the actions to be taken in the event of either theft or damage in both procedures and contracts;
- Ensure that all staff, (including contractors), handling and managing these products are carefully vetted, specially trained and understand their duties and responsibilities with respect to national and international legislation;
- Maintain detailed records and control documentation in line with the guidelines in Chapter 4;
- Utilise access controls, alarms and CCTV monitoring where possible;
- Establish *Bona fides* of all suppliers, customers (including collection and delivery addresses) and supply chain partners and repeat this verification on a regular basis, addressing any non-conformances in a timely fashion;
- Create and keep up to date a list of at least three individuals and mobile phone numbers on which they can be contacted at any time (24/7); **Note:** time is critical if an issue arises, especially over a weekend or 'out of hours'.

9.4. Products requiring special conditions ((ii) Temperature sensitive products)

For temperature-sensitive products, qualified equipment (e.g. thermal packaging, temperature-controlled containers or temperature-controlled vehicles) should be used to ensure correct transport conditions are maintained between the manufacturer, wholesale distributor and customer.

What is the rationale for this point of guidance?
If the equipment used is not qualified then the products may be adversely affected during transit.

What are the benefits and risks associated with this point of guidance?

Benefits
- The quality of temperature-sensitive products is maintained;
- Having a robust approach to qualification will provide proof of suitability to both regulators and customers.

Risks
Without the assurance of such qualification, defective products might unknowingly enter the supply chain.

Implementation
Consider the options available such as:
- Temperature-controlled vehicles;
- Active or passive packaging solutions.

Arrange qualification to prove the suitability of the selected solution.
Packaging qualification exercises involve understanding of:
- Minimum/Maximum loads;
- Tailored thermal profiles representing required seasonal extremes (climatic chamber profiles (based upon ISTA procedure 7D (2007))); the profile choice should reflect anticipated extremes of temperature at shipping and receiving locations;
- Likely 'worst case scenarios' for timings of each leg of the journey taking account of transport and customs delays;
- The potential risks to products arising from vibration or compression. The qualification should include testing if risk is identified.

Document the results of the qualification studies which have been carried out. Obtain ongoing assurance through real-time temperature monitoring placing data loggers and probes at product level during each shipment.

Note:
- Conditions will vary throughout containers, so placements should be chosen to be representative of those to which the product will be exposed;
- Accurate data loggers are now widely available and are inexpensive in relation to the value of medicinal product shipments. Given that every shipment is unique and it is not possible to fully ensure against events such as doors being left open or product being left outside for periods of time during loading and unloading procedures, they can provide invaluable data and are recommended for all temperature-sensitive shipments.

9.4. Products requiring special conditions ((iii) Temperature controlled vehicles)

If temperature-controlled vehicles are used, the temperature monitoring equipment used during transport should be maintained and calibrated at regular intervals. Temperature mapping under representative conditions should be carried out and should take into account seasonal variations.

What is the rationale for this point of guidance?
Calibration: If equipment is not calibrated correctly, then the data it produces cannot be relied on.

Seasonal mapping: If the effect of seasons is not taken into account, then the information may provide a false sense of security.

What are the benefits and risks associated with this point of guidance?
Refer to that provided for the use of qualified equipment.

Implementation
Calibration:
- Calibrate equipment according to written procedures and an established schedule as stated in clause 5.3 of EU GMP Part II guidelines; Note: A maximum 12-month calibration interval is normally selected but could be tighter where experience or the equipment supplier requires it;
- Implement a calibration schedule which avoids the calibration status of devices expiring. Section 3.3 of EU GDP also refers to calibration and states a requirement for equipment to be calibrated at defined intervals based upon a risk and reliability assessment;
- Ensure that devices are calibrated over an appropriate range for the required environment(s).

Note 1: Probes should be calibrated to traceable National or International Standards, such as UKAS (United Kingdom Accreditation Service) or NIST (National Institute of Standards and Technology).
Note 2: Probes should ideally be flexible and long enough to be placed into a dry block calibrator so that they can be exposed to conditions across the chosen range and calibrated in situ. If this is not possible, then a reference device can be placed directly next to the probe but this only provides the option of a single point calibration. Multi-point calibration demonstrates accuracy across the range of the environment and should identify the risk of control failures, such as frozen stock, which could be caused by varying temperatures which can occur in large containers if combined with a low set point, e.g., 2°C.

Vehicle mapping:
- Carry out vehicle mapping when documented risk assessment shows the widest range in temperature and humidity; typically, Summer and Winter;
- Repeat the mapping whenever significant modifications are made to the temperature control equipment or vehicle;
- Document any corrective actions or retests for vehicles that fail the mapping test(s)
- Understand the accuracy of recording and control equipment in order to ensure that the required temperature is maintained;

Note 1: The tolerance (accuracy) of the calibration should be available on the certificate.
Note 2: Understanding this accuracy is important in helping to evaluate the implications of any failures and/or deviations. e.g. If temperature excursions are such that product rejection is required, this information will play a part in

establishing where liability lies in respect of a possible insurance claim.
- Adopting a 'multi-point' approach to the siting of control probes is very important.

Refer to Appendix 2, Section 9.4 (iii) for additional detailed guidance on the implementation of effective mapping.

9.4. Products requiring special conditions ((iv) Demonstration of control)

If requested, customers should be provided with information to demonstrate that products have complied with the temperature storage conditions.

What is the rationale for this point of guidance?

Various interested parties within the supply chain may require, or wish, to receive this information to meet GDP, legal or business needs.

What are the benefits and risks associated with this point of guidance?

Benefits
- Prompt provision of information to meet customer requests will facilitate supplies to patients and improve customer satisfaction.

Risks
- Without planning, the provision of information can be delayed, which can interrupt supplies and result in customer complaints and / or delays to a patient receiving treatment.

Implementation
- Ensure that vehicle temperature records are printed, reviewed and signed by the recipient (to confirm their acceptability) and archived;
  Note: Vehicle temperature records may not be fully representative of the conditions the product has been exposed to, due to the monitoring probes being at a different level in the vehicle or to periods during which pallets/containers are outside the vehicle. So, data logger printouts or electronic files should also be reviewed and provided on request;
  Note: Ensure that the archived records will be accessible and readable throughout the required retention period. This may entail the scanning and electronic storage of printouts to safeguard against fading over time;
- Minimise the duration of any periods out of controlled storage and set limits based on criticality to the product. Limits may be for a single excursion or cumulative, or a combination of both. The limits should be based on stability data, agreed with the Marketing Authorisation Holder and specified in contracts;
- Review data regularly for any trends that might point to risk of location/ route failures.

9.4. Products requiring special conditions ((v) Use of cool packs)

If cool-packs are used in insulated boxes, they need to be located such that the product does not come in direct contact with the cool-pack. Staff must be trained on the procedures for assembly of the insulated boxes (seasonal configurations) and on the reuse of cool-packs.

There should be a system in place to control the re-use of cool-packs to ensure that incompletely cooled packs are not used in error. There should be adequate physical segregation between frozen and chilled ice packs.

What is the rationale for this point of guidance?
- These requirements relate to the use of insulated boxes with cool packs which utilise passive cooling to maintain the product temperature, usually between +2°C to +8°C for 24 to 72 hours;
- Direct contact of a cool pack could result in any liquid contents being frozen which could then degrade or destabilize the product;
- Cool packs require acclimatisation for a minimum period of time before being used to pack an insulated container. This period can be long and it is not easy to detect that there has been insufficient acclimatisation during packaging, so a detailed process should be in place to provide assurance;
  Note: Although this section only mentions cool packs, the principles are also valid for controlled ambient temperature products, where 'warm packs' are used instead of cool packs.

What are the benefits and risks associated with this point of guidance?

Benefits
- The use of a combination of insulated boxes and cool packs is an efficient method of transporting temperature-sensitive products in small to medium sized quantities for periods of up to 72 hours;
- Avoidance of degradation or destabilization of the product resulting from freezing;
- The reuse of boxes and cool packs reduces costs – see below for a Risk.

Risks
- If fully and part frozen cool packs are mixed, then this could adversely affect the performance of the box/cool pack combination and consequently the quality of the product;
- If insulated boxes and other components are not checked by trained personnel for damage before re-use, the effectiveness of the box may be impacted, leading to failure to maintain temperature requirements and consequent impact on product quality;
- Re-use of insulated boxes and other components is acceptable,

but needs to be controlled to ensure that performance of the pack is maintained. In addition to evident damage, the performance of insulating materials may degrade over time;
- Leakage from cool packs could contaminate product.

Implementation
- Gather knowledge on the likely duration of shipments, with allowance for delays, and the extremes of temperature likely to be encountered and use this to devise the packaging combination;
- Create a procedure with:
  - diagrams detailing the packaging configurations for the insulated boxes for different shipments at different times of the year;
  - the process for freezing (or other pre-conditioning) of the cool packs;
  - requirements relating to potential reuse of cool packs and other components, including checks for cracks, dents, holes etc., in the insulated box, and leaks or signs of leakage with the cool packs. Certain components may need to have reuse restricted by number of shipments or time as even in the absence of evident physical damage their performance may degrade. Take account of manufacturers' recommendations;
- Test (validate) the packaging combinations to demonstrate the period of time for which they will maintain the required product conditions under the defined extremes of external temperatures;
- It is likely that different configurations will be required for different seasons since these will typically have different external temperature challenges. The procedure should be clear as to which configuration should be used at different times during the year;
- Ensure that a defined and documented process (SOP) is in place for stock rotation of cool packs. There are many ways to do this depending on how long the cool packs need to be conditioned for, but some examples are:
  - provide five shelves in the freezer and label each one with days of the week Monday – Friday. Use the Ice-packs from the current day and then re-fill the shelf at the end of the day or first thing the following day;
  - provide two zones in the freezer, load packs into zone 1 and then transfer to zone 2 after HH hours, with HH determined by validation. Only use zone 2 cool packs to pack insulated containers:
  - when cool packs are loaded into the freezer, use a date stamp to mark the date of entry. Cool packs can only be used for DD number of days after the stamped entry date;
  - the use of an infrared temperature gun which can be used to check the cool packs before use.

Figure 8: Photographs are very helpful to staff and complement packing configuration diagrams

9.4. Products requiring special conditions ((vi) Delivery of sensitive products and seasonal variations)

The process for delivery of sensitive products and control of seasonal temperature variations should be described in a written procedure.

What is the rationale for this point of guidance?

Seasonal temperature variations can have a huge impact on the distribution of temperature sensitive products. For example, temperatures in Southern Europe or the Middle East can reach 50°C in summer months and in Northern Europe and Northern America temperatures drop below -20°C during winter. Similarly, temperatures can range widely between day and night. For example, in desert areas in the Middle East temperatures may drop to freezing during the night in some seasons. Further, some countries, e.g., China, are so large that they can experience an extremely wide range of conditions.

What are the benefits and risks associated with this point of guidance?

Benefits

By having a documented process which accounts for seasonal variations when defining the shipping methods to be used for temperature-sensitive products, the risk of temperature excursions will be minimised.

Risks

If no attention is paid to seasonal temperature variations, the risk of temperature excursions will increase dramatically. For example, an insulated

container with a packaging configuration validated for winter use will not maintain the temperature of 2°C to 8°C product for as long in the summer. Similarly, a product with a 'Do not freeze' label will require extra protection if being transported on an uncontrolled vehicle in the middle of winter.

Implementation

- Understand the conditions which prevail at each stage of each period throughout the supply chain at the possible extremes of temperature and humidity;
- Understand the sensitivity of the product to variations by reference to the MA Holder;
- Select a packaging system and transit process which will maintain good control;
- Anticipate the use of different shipping methods to cope with seasonal variations;
- Detail this in a procedure. This procedure should include:
  - the packaging specification to be used, which accommodates the expected journey time(s) and expected external temperatures;
  - a nominated person should have responsibility and authority for deciding when a change in packaging system and/or transit process is required to ensure compatibility with the expected environmental conditions. e.g. when to switch from a Summer to a Winter packaging system;
  - the type of insulated box to be used for the expected journey time and amount of product being shipped;
  - the use of the cool packs e.g.
    - the temperature at which they should be conditioned;
    - the length of time required for;
    - the process for identifying how long they have been conditioned which will involve rotation;
    - the exact locations in which they should be placed in the insulated box;
    - any precautions required to prevent the cool packs coming into direct contact with product, e.g., insulation, void filler, bubble-wrap;
    - the reuse of components;
    - checks required for damage;
    - the method for reconditioning cool packs.

Chapter 10 – Specific Provisions for Brokers

10.1. Principle

A 'broker' is a person involved in activities in relation to the sale or purchase of medicinal products, except for wholesale distribution, that do not include physical handling and that consist of negotiating independently and on behalf of another legal or natural person [(2)].

Brokers are subject to a registration requirement. They must have a permanent address and contact details in the Member State where they are registered [(3)]. They must notify the competent authority of any changes to those details without unnecessary delay.
By definition, brokers do not procure, supply or hold medicines. Therefore, requirements for premises, installations and equipment as set out in Directive 2001/83/EC do not apply. However, all other rules in Directive 2001/83/EC that apply to wholesale distributors also apply to brokers.

(2) Article 1(17a) of Directive 2001/83/EC.

(3) Article 85b of Directive 2001/83/EC.

What is the rationale for this point of guidance?

This Chapter delivers the requirement of Article 85b (3) of Directive 2001/83/EC. Prior to the amendment of Directive 2001/83/EC by Directive 2011/62/EU, there were no requirements for brokers of medicinal products to be registered with the competent authority of the Member State in which they were located and there was a general lack of visibility of their activities. This presented a potential weakness in the supply chain for the entry of falsified medicines.

There was also a lack of clarity regarding what a broker was, how their activities differed from wholesale dealing and what constituted good practice for these activities.
This chapter of GDP guidance sets out to clarify the role and responsibilities of brokers and the quality standards expected from them.

10.2. Quality System

The quality system of a broker should be defined in writing, approved and kept up-to-date. It should set out responsibilities, processes and risk management in relation to their activities.

The quality system should include an emergency plan which ensures effective recall of medicinal products from the market ordered by the manufacturer or the competent authorities or carried out in cooperation with the manufacturer

or marketing authorisation holder for the medicinal product concerned [4]. The competent authorities must be immediately informed of any suspected falsified medicines offered in the supply chain [5].

(4) Article 80(d) of Directive 2001/83/EC.

(5) Article 85b(1), third subparagraph of Directive 2001/83/EC

What is the rationale for this point of guidance?
The quality system in any organisation should be seen as a key business process which defines the controls required for the activities performed by the company. An appropriately designed quality system will define the roles and responsibilities of the company in relation to its customers and supplier(s) as well as its staff.

Defective or falsified medicinal products can pose a significant threat to public health and it is therefore important that defective medicines can be promptly recalled and that suspicions of falsified medicines can be quickly investigated. Brokers, being the interface between customers and manufacturers/marketing authorisation holders, play a key role in helping to ensure appropriate communications and actions with both these parties and the competent authorities. Consequently, the quality system should include processes for dealing with these situations.

Implementation
- Develop a quality system based on the principles of ISO 9001 and Chapter 1 - QMS. It should include the following key elements:
  - Scope of the operations, i.e. to facilitate procurement of medicines, but not to purchase, hold or distribute them;
  - Definition of the roles and responsibilities for personnel in the company
  - Staff selection recruitment and training;
  - Documentation and records, including contact details of customers and suppliers;
  - Management review – monitoring of performance and controls within the scope of operations;
  - Customer expectations;
  - Customer bona fides;
  - Supplier bona fides;
  - Product recall;
  - Customer complaints;
  - Continuous improvement;
- Describe this system in a Quality Manual which refers to the policies, procedures, instructions and records required to run the business effectively;
- See Section 10.4 for further details regarding recalls and suspected falsified medicinal products.

10.3. Personnel
Any member of personnel involved in the brokering activities should be trained in the applicable EU and national legislation and in the issues concerning falsified medicinal products.

What is the rationale for this point of guidance?
The procurement and sale of medicinal products frequently involves a complex process which is vulnerable to the criminal insertion of falsified medicines from unauthorised suppliers or sale to unauthorised recipients. In order to safeguard the legitimate supply chain, it is therefore important for personnel with responsibilities for purchasing and selling medicinal products to have a good understanding of the EU legislative requirements on such matters and know the risks and how to avoid them.

Implementation
Staff training should include:
- How to check bone fides of both suppliers and potential customers;
- An overview of the Falsified Medicines Directive (2011/62/EU);
- Understanding of risk scenarios. e.g.:
  - Products are offered in relatively high volumes at short notice when there is a market shortage;
  - Products are offered at unusually low prices;
- How to access local regulatory authority notices on recent falsified medicines identified in the country;
- An understanding any specific local/regional requirements and risk in relation to falsified medicinal products.

10.4. Documentation
The general provisions on documentation in Chapter 4 apply.
In addition, at least the following procedures and instructions, along with the corresponding records of execution, should be in place:
- (i) Procedure for complaints handling;
- (ii) Procedure for informing competent authorities and marketing authorisation holders of suspected falsified medicinal products;
- (iii) Procedure for supporting recalls;
- (iv) Procedure for ensuring that medicinal products brokered have a marketing authorisation;
- (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;

(vi) Records should be kept either in the form of purchase/sales invoices or on computer, or in any other form for any transaction in medicinal products brokered and should contain at least the following information: date; name of the medicinal product; quantity brokered; name and address of the supplier and the customer; and batch number at least for products bearing the safety features.

Records should be made available to the competent authorities, for inspection purposes, for the period stated in national legislation but at least five years.

What is the rationale for this point of guidance?
Complaints are a key mechanism for identifying issues and provide an opportunity to identify the root cause and take action to prevent recurrence. In the worst case, complaints might lead to the identification of issues that require a product recall. It is therefore important that there is a procedure in place that promptly deals with complaints and enables a link to be made between customers and suppliers.

Falsified medicines pose a potentially serious threat to public health and it is important that both competent authorities and marketing authorisation holders are made aware of any suspicions so that appropriate investigations can be carried out and action taken where appropriate.

Brokers manage procurement and supply of medicinal products and have links to both the manufacturer and the purchasers of these products. Therefore, in the event of a product recall, they should be able to contact their customers promptly informing them of the reason for the recall and what action has been agreed between the Marketing Authorisation holder and the regulator(s).

The process of marketing authorisation is fundamental to ensuring that only products that have demonstrated quality, safety and efficacy are supplied to patients. Brokers, as part of the supply chain, need to ensure that they are only dealing with authorised products.
The security of the medicinal product supply chain is founded on the assurance that both suppliers and customers are duly authorised.

Good record keeping is a business necessity; companies need to have these records to perform effectively and legally. The records listed are the minimum requirements to enable appropriate investigation and action should any issues arise, so they should be made accurately at the time of the activity and kept securely. Since action may need to be taken promptly, it is important that the records are easily accessible.

Implementation
A complaint procedure should include:

- How to receive a complaint, evaluate it and communicate with the marketing authorisation holder(s);
- Requirements for recording complaints received, including details of the product/batches involved and the name and address of the complainant;
- How to investigate, identify the root cause and report the findings;
- How to monitor progress until resolution of the issue;
- Developing corrective and preventive actions to address the immediate issue and also prevent recurrence.

A procedure for dealing with suspected falsified medicinal products should include:

- How to identify a falsified medicine;
- Contact details of the competent authority;
- Contact details of all manufacturers/marketing authorisation holders the company is dealing with;
- How to maintain records of all purchase and sales activities.

An effective recall procedure will include:

- A list of contacts for Marketing Authorisation Holders – often the manufacturers;
- An understanding of how Marketing Authorisation Holders will communicate a potential recall to them and their expectations;
  Note: this information should be defined in Quality/Technical Agreements;
- Contact details (contact name, address, email and telephone numbers) of their customers, including 'out of hours';
- How to maintain and access records which detail the batch number of all products procured and supplied;
- A process for establishing which customers have been supplied with affected product batches;
- A description of how to contact the customers promptly;
- A description of how to contact local regulatory authorities;
- A process for testing the recall system annually using a mock example.

The process for checking that medicinal products have a marketing authorisation should:

- provide links to available local authority published lists, or the EMA website for appropriate products and manufacturers;
- explain how to request MA and MIA numbers from the suppliers, or a copy of the certificates published by the competent authorities and/or EMA.

Verification of suppliers and customers can be achieved using the following sources:

- GDP certificates for European wholesalers are listed in the EudraGMDP site;
- GMP certificates for manufacturers are listed in the EudraGMDP site;
- Majority of the European competent authorities publish lists of authorised wholesalers and MIA holders and of authorisations which have recently been withdrawn, - check local authority websites;
- Request a copy/confirmation of the WDA and GDP certificate from the wholesaler and MIA and GMP certificate from the manufacturer/importer at a regular frequency. Check for any local regulatory expectations on frequency. Note: UK MHRA guidance is that "There should be a procedure that ensures there are documented checks made at least twice a month of MHRA's list of suspended licence holders and regular checks on EudraGMDP website for issued GMP and GDP statements of non-compliance."

Refer to Chapter 4 of this document for further guidance on good documentation practices and record keeping.

Glossary - Abbreviations

Abbreviation	Full wording	Supplementary information
3PL	Third Party Logistics	The use of a third party business to outsource elements of distribution services.
ALCOA+ (also termed 'ALCOA CCEA' to spell out the 'plus' elements)	Attributable Legible Contemporaneous Original (or True Copy) Accurate Complete Consistent Enduring (Permanent) Available	Requirements for data integrity; see Chapter 4
ASN	Advanced Shipping Notice	A document, usually sent in electronic format, that provides detailed information about a pending delivery. The purpose of an ASN is to notify the customer when shipping occurs and provide physical characteristics about the shipment and its mode of transportation so the customer can be prepared to accept delivery.
(N)CA	(National) Competent Authority	The body / agency with responsibility for the regulation of medicines at a national level. A list of national competent authorities in the EEA may be found on the EMA website.
CAPA	Corrective and Preventive Actions	See separate entries in Definitions section`
CMP	Continuous Monitoring Probes	
DQ	Design Qualification	The step in the validation life cycle providing documented verification of compliance of the design with the requirements of the User Requirements Specification (URS).

EEA	European Economic Area	The group of countries, comprising the 28 member states of the European Union (EU) together with Iceland, Liechtenstein and Norway, covered by an agreement allowing the free movement of persons, goods, services and capital between them.
EMA	European Medicines Agency	The agency responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU. http://www.ema.europa.eu/ema
FEFO	First Expiry, First Out	
GDP	Good Distribution Practice	
GMP	Good Manufacturing Practice	
GSL	General Sales List medicine	
HVAC	Heating, Ventilation and Air Conditioning	
IQ	Installation Qualification	The step in the validation life cycle providing documented verification that equipment, facilities or systems are installed in compliance with the approved design and manufacturer's recommendations. (Based on EudraLex Volume 4, Annex 15)
KPI	Key Performance Indicators	
MAH	Marketing Authorisation Holder	
MIA	Manufacture / Import Authorisation	
OQ	Operational Qualification	The step in the validation life cycle providing documented verification that equipment, facilities or systems as installed perform as intended throughout the anticipated operating range. (Based on EudraLex Volume 4, Annex 15)
P	Pharmacy Only medicine	
POD	Proof of Delivery	
POM	Prescription Only Medicine	
PQ	Performance Qualification	The step in the validation life cycle providing documented verification that equipment, facilities or systems as installed perform effectively and reproducibly when operated according to the approved procedure. (Based on EudraLex Volume 4, Annex 15)
PV	Pharmacovigilance	
QMS	Quality Management System	
RACI chart	Responsible Accountable Consulted Informed	A table detailing different roles and responsibilities for different activities
QP	Qualified Person	
QRM	Quality Risk Management	
QTA	Quality/Technical Agreement	
RFID	Radio Frequency Identification	
RP	Responsible Person	
SOP	Standard Operating Procedure	
SSCC	Serial Shipper Container Code	An 18-digit code in a GS1 barcode format or radio frequency identification (RFID) tag which identifies the manufacturer/supplier and packaging unit.

URS	User Requirements Specification	The specification for equipment, facilities, utilities and processes that defines the essential quality elements required and provides a point of reference throughout the validation life cycle. (Based on EudraLex Volume 4, Annex 15)
WDA	Wholesale Distribution Authorisation	The required authorisation, issued by the national competent authority, for organisations engaged in the distribution of medicinal products. NOTE: Historically there has been some variation in the word assigned to the 'D', with Dealer's and Distributor's also being used.

Glossary - Definitions

Audit trail
An audit trail is a chronological record, set of records, and/or destination and source of records that provide documentary evidence of the sequence of activities that have affected at any time a specific operation, procedure, or event.

Bona fides
Checking the legitimacy of an organisation to purchase or sell medicinal products.

Broker
A 'broker' is a person involved in activities relating to the sale or purchase of medicinal products, except for wholesale distribution, that do not include physical handling of the medicines.

Business Continuity (Management) Plan
Business continuity planning is the process of creating systems of prevention and recovery to deal with potential threats to a company.

Certificate of Analysis
A document generated by the MAH listing all the results of the tests performed on a batch of medicinal product.

Change Control
Process of initiating, reviewing, evaluating and approval of changes to processes, systems and facilities in a GDP environment.

Cold chain
Refers to process of storage and transportation of medicinal products at 2 – 8 °C

Complaint
An expression of dissatisfaction related to product or service by the customer.

Continuous improvement
Ongoing effort to improve, products, services, and processes.

Contract
A contract is an arrangement between two or more parties that is enforceable by law as a binding legal agreement.

Contract Acceptor
The person or an organisation which accepts the responsibilities and actions defined in the contract.

Contract Giver
The person or organisation which defines the expectations in the contract.

Corrective Action (see also CAPA and Preventive Action)
Action to eliminate the cause of a detected nonconformity.

Deviation
Departure from a procedure or standard.

Disaster Recovery Plan
A plan for recovering an operation following a disaster. Especially used in relation to IT systems.

Falsified Medicine
Falsified medicines are fake medicines that pass themselves off as real, authorised medicines. Falsified medicines might contain ingredients, including active ingredients, which are of bad quality or in the wrong dose – either too high or too low. As they have not been properly evaluated to check their quality, safety and efficacy - as required by strict EU authorisation procedures - this could be detrimental to health. Falsified medicines are a major threat to public health (the term "falsified" refers to all forms of falsification, while the term "counterfeit" specifically refers to an infringement to intellectual property rights).
Ref.: European Commission; https://ec.europa.eu/health/human-use/falsified_medicines_en

Job Description
A job description is a document that describes the general tasks, or functions, and responsibilities of a position.

Management Review
Process of reviewing the company's performance against set objectives by the management team.

Narcotic
Originally, any drug derived from opium or opium-like compounds with potent analgesic effects associated with both significant alteration of mood and behavior and with potential for dependence and tolerance, this term is now used more widely for any drug, synthetic or naturally occurring, with effects similar to those of opium and opium derivatives, including meperidine, fentanyl, and their derivatives.
Ref. Farlex Partner Medical Dictionary

Packaging
The carton or box that the product is placed in for transportation. It could be a cardboard carton, validated insulated shipper, tote box etc.

Parallel import
Importation of a product within the European Union which was originally sold in another member state.

Preventive Action (see also CAPA and Corrective Action)
Action to eliminate the cause of a potential nonconformity.

Quality Assurance (QA)
The maintenance of a desired level of quality in a service or product, especially by means of attention to every stage of the process of delivery or production.

Quality Control (QC)
Is a procedure or set of procedures intended to ensure that a manufactured product or performed service adheres to a defined set of quality criteria or meets the requirements of the client or customer. QC is similar to, but not identical with, quality assurance (QA).

Quality Manual
A quality manual is the main, top-level document of a quality management system it establishes the policy level position of a company in relation to its products and services.

Quality Policy
Is a document developed by management to express the directive of the top management with respect to quality.

Recall
Withdrawal of a product or batch(es) of product from market.

Reefer
Refrigerated transport.

Root Cause Analysis
Identifying the fundamental cause (reason) of the occurrence of a deviation.

Segregation
Physical separation of products or activities, where there is no contact.

Shipping container
A shipping container is the vessel that is used to transport a product. It could be a lorry, van, reefer, 20ft (6.5m) / 40ft (13m) steel container or active temperature control box. See section 9.3 for more details.

'Time at ambient temperature' (TAT)
Duration of period product remains at ambient temperature.

Validation
Action of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results.

Bibliography (and other useful links)

Biomap (with thanks to Kane Edgeworth)

Temperature mapping protocol template (2016)
Temperature mapping report template (2016)
Example templates for temperature mapping activities available free of charge from the ECA website or the PQG shop (via the PQG website)

Cogent

Responsible Person Gold Standard (2014):
http://www.thegold-standard.co.uk/job-details/?jobid=297
Developed by industry with the support of the UK MHRA, this sets out the key Technical, Compliance, Business Improvement and Functional & Behavioural knowledge and competency expectations of Responsible Persons.

ECA (European Compliance Academy)

Main website: http://www.gmp-compliance.org/
Code of Practice for Responsible Persons:
http://www.good-distribution-practice-group.org/gdp-code-of-practice-rps.html
Accessible after free registration.

ECA (European Compliance Academy)/PQG (Pharmaceutical Quality Group)

Self inspection checklist (2016)
Self inspection SOP template (2016)
Example templates for self inspection activities available free of charge from the ECA website or the PQG shop (via the PQG website)

EMA (European Medicines Agency)

Q&A on data integrity (2016):
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp&mid=WC0b01ac05800296ca#section16
Although directed at pharmaceutical manufacturers to help meet the fundamental requirements in EU GMP (EudraLex Volume 4), these Q&A are nonetheless worth looking at and it is likely that future revisions will have a wider GxP scope.

EudraGMDP database

Main database home page:
http://eudragmdp.ema.europa.eu/inspections/displayHome.do
GDP home page:
http://eudragmdp.ema.europa.eu/inspections/view/common/GDPHomePage.xhtml
From here, both GDP certificates and non-compliance reports can be accessed.

EudraLex - EU Legislation
http://ec.europa.eu/health/documents/eudralex_en

Volume 1 - EU pharmaceutical legislation for medicinal products for human use
http://ec.europa.eu/health/documents/eudralex/vol-1_en

Volume 4 - Guidelines for good manufacturing practices for medicinal products for human and veterinary use
http://ec.europa.eu/health/documents/eudralex/vol-4_en

- EU GMP Annex 11: Computerised Systems
  http://ec.europa.eu/health/files/eudralex/vol-4/annex11_01-2011_en.pdf
- EU GMP Annex 15: Qualification and Validation
  http://ec.europa.eu/health/files/eudralex/vol-4/2015-10_annex15.pdf
- EU GMP Part II: Basic Requirements for Active Substances used as Starting Materials
  https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2014-08_gmp_part1.pdf
- EU GMP guidance on Site Master Files:
  http://ec.europa.eu/health/files/eudralex/vol-4/2011_site_master_file_en.pdf

European Commission

Guidelines on Good Distribution Practice of medicinal products for human use (2013/C 343/01), November 2013:
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:343:0001:0014:EN:PDF

Good Distribution Practice for Medicinal Products for Human Use – Questions and Answers, Version 1.0
Ares(2014)968163 - 28/03/2014
https://ec.europa.eu/health/sites/health/files/files/gdp/2014-04_qas_.pdf

Falsified Medicines
The Commission has a web page specifically covering falsified medicines at
http://ec.europa.eu/health/human-use/falsified_medicines_en

This includes a Q&A document on safety features (Version 9, February 2018)
https://ec.europa.eu/health/sites/health/files/files/falsified_medicines/qa_safetyfeature_v9.pdf

European Union

Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data:
http://ec.europa.eu/justice/policies/privacy/docs/95-46-ce/dir1995-46_part1_en.pdf

Directive 2001/83/EC on the Community code relating to medicinal products for human use
Originally of 06-Nov-2001, this Directive has been amended by 12 subsequent pieces of legislation as at 01-Jun-2017 and it is recommended that the consolidated text is accessed via EudraLex Volume 1:
https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

Directive 2011/62/EU amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products:
https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf

Guideline 2013/C 343/01 on Good Distribution Practice of medicinal products for human use:
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:343:0001:0014:EN:PDF
This is the text on which this ECA/PQG Guideline is based.

Regulation (EU) 2016/161 supplementing Directive 2001/83/EC ... by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use:
http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:L:2016:032:FULL&from=EN

Global Harmonization Task Force (Now, International Medical Device Regulators Forum)
http://www.imdrf.org/

GHTF SC3: Quality Management System – Medical Devices – Guidance on corrective action and preventive action and related QMS processes (Nov 2010)
http://www.imdrf.org/docs/ghtf/final/sg3/technical-docs/ghtf-sg3-n18-2010-qms-guidance-on-corrective-preventative-action-101104.pdf

International Conference on Harmonisation (ICH)
http://www.ich.org

ICH Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q7/Step4/Q7_Guideline.pdf

ICH Q9: Quality Risk Management
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf

ICH Q10: Pharmaceutical Quality System
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf

International Safe Transit Association (ISTA)
https://www.ista.org

Procedures may be found at
http://ista.org/test_procedures.php
and include the procedure referenced in Section 9.4(ii):

Procedure 7D: Thermal Controlled Transport Packaging for Parcel Delivery System Shipment
Basic Requirements: atmospheric conditioning, vibration and shock testing (2007)

International Society for Pharmaceutical Engineering (ISPE)
https://www.ispe.org/home

Direct link to publications page:
https://www.ispe.org/publications-guidance-documents
ISPE produce a number of guides which may be of help in the design, validation and maintenance of facilities, including a 'Baseline® Pharmaceutical Engineering Guide on 'Commissioning and Qualification' and Good Practice Guides on 'Heating, Ventilation and Air-Conditioning (HVAC)' and 'Packaging, Labeling and Warehousing Facilities'. They also publish

GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems (2008)

International Standards Organisation (ISO) Standards Catalogue
https://www.iso.org/standards-catalogue/browse-by-ics.html

ISO 9000:2015 'Quality management systems -- Fundamentals and vocabulary'

ISO 9004:2009 'Managing for the sustained success of an organization -- A quality management approach'

ISO 19011:2011 'Guidelines for auditing management systems'

Also of interest will be the website below which provides a gateway to information on the ISO 9000 document series:
http://www.iso.org/iso/home/standards/management-standards/iso_9000.htm

Medicines and Healthcare products Regulatory Agency (MHRA) (UK)
https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency

Authorisation/Licensing
MHRA statement (2014) regarding need for depots, freight consolidators and freight forwarders to be licensed. http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodManufacturingPractice/News/CON447997

Blog
https://mhrainspectorate.blog.gov.uk/
This Blog is authored by the Inspectorate division and covers all good practice (GxP) disciplines.

There is a search function on the blog and entering 'GDP' here will help rapid identification of GDP-related topics. It is also possible to sign up to an alerting service which will send you an email as new posts are made.

Brokers
MHRA Advice to brokers (and list of registered brokers):
http://www.mhra.gov.uk/Howweregulate/Medicines/Overviewofmedicineslegislationandguidance/TheFalsifiedMedicinesDirective/Brokersoffinishedmedicinalproducts/index.htm

Data integrity guidance
'GXP' Data Integrity Guidance and Definitions (March 2018)
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/687246/MHRA_GxP_data_integrity_guide_March_edited_Final.pdf

Good Practice Guides
Rules and Guidance for Pharmaceutical Manufacturers and Distributors ('Orange Guide')
Rules and Guidance for Pharmaceutical Distributors ('Green Guide')
Published by the Pharmaceutical Press http://www.pharmpress.com/ and also available through online services such as Medicines Complete https://www.medicinescomplete.com/mc/

Inspections
General information on how to Comply with good manufacturing practice (GMP) and good distribution practice (GDP), and prepare for an inspection
https://www.gov.uk/guidance/good-manufacturing-practice-and-good-distribution-practice

Deficiency data
MHRA issue periodic reports analysing their deficiency data. The best way to find the most recent data will be via the Blog (see above)

Returns
MHRA guidance on returns:
http://www.aah.co.uk/sites/default/files/MHRA%20guidelines%20-%20returning%20of%20non-defective%20goods.pdf

Suspended and revoked licences for manufacturers and wholesalers of medicines
https://www.gov.uk/government/publications/suspended-licences-for-manufacturers-and-wholesalers-of-medicines

Pharmaceutical Inspection Co-operation Scheme (PIC/S)
https://picscheme.org/

PI 006-3 (2007): Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation, Cleaning Validation
https://picscheme.org/layout/document.php?id=152

Pharmaceutical Quality Group (PQG)
http://www.pqg.org/pharma/
The PQG Shop can be accessed from this home page.

UK Home Office

Security guidance for all existing or prospective Home Office Controlled Drug Licensees and/or Precursor Chemical Licensees or Registrants (2016)
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/526557/Security_Guidance_for_all_Businesses_and_Other_Organisations-_Final-_May_2016.pdf

World Health Organisation (WHO)
http://www.who.int

Guide to good storage practices for pharmaceuticals (2003)
WHO Technical Report Series, No. 908, Annex 9, 2003
http://www.who.int/medicines/areas/quality_safety/quality_assurance/GuideGoodStoragePracticesTRS908Annex9.pdf?ua=1

Supplementary guidelines on good manufacturing practices: validation (2006)
WHO Technical Report Series, No. 937, Annex 4, 2006
http://www.who.int/entity/medicines/areas/quality_safety/quality_assurance/SupplementaryGMPValidationTRS937Annex4.pdf?ua=1
Change control is specifically dealt with in Section 12 of this Annex (p118 – 119)

Good distribution practices for pharmaceutical products (2010)
WHO Technical Report Series, No. 957, Annex 5, 2010
http://www.who.int/medicines/areas/quality_safety/quality_assurance/GoodDistributionPracticesTRS957Annex5.pdf

Guidance on good data and record management practices (2016)
WHO Technical Report Series, No. 996, Annex 5, 2016
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf?ua=1

Appendices

APPENDIX 1: OUTLINE CONTRACT FOR USE IN GDP OUTSOURCING

DISCLAIMER: This outline is provided in order to prompt consideration and give additional guidance on content. It is stressed that every Contract Giver – Contract Acceptor arrangement is unique and should therefore be subject to an appropriately customised Quality/Technical Agreement with input from relevant staff from both parties. ECA and PQG take no responsibility for any Quality/Technical Agreements that may be created based on this outline.

QUALITY/TECHNICAL AGREEMENT Between

(1) Contract Giver details, including licence holding details

(2) Contract Acceptor details, including licence holding details

Signed

(1)		Date
(2)		Date

Review Date: X years from final signature date

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1 Definitions

Unless otherwise specifically provided in this Agreement, the following terms shall have the following meanings:

EXAMPLES:	
Applicable Laws and Regulations	with respect to each Product, means all supranational, national, and local laws, and the rules, regulations, guidances, guidelines and requirements of all Regulatory Authorities in effect from time to time applicable to the handling of such Product in Territory including applicable cGMP principles and GDPs.
Distribution	With respect to each Product means all processes related to the handling from receipt of order up to customer invoicing.
FMD	Falsified Medicines Directive (EU/EEA applicable)
Service Provider Procedures	means Service Provider's written standard operating procedures in full compliance with Applicable Laws and Regulations.

2 Introduction and Scope

Detail in this section, for example,

- The purpose and scope of the agreement,
- Business expectations,
- Renewal period for QTA and responsibilities for update
- Responsibilities for maintaining licenses/approvals etc. for contracted services
- Reference to a separate commercial agreement including any legal and financial statements (including any compensation clauses for damages, poor performance etc).
- Confidentiality arrangements

3 General

Example clauses:

3.1 Service Provider shall conduct all contracted activities in compliance with all applicable Laws and Regulations, the applicable Product Requirements and Service Provider Procedures.

3.2 Service Provider shall, among other things ensure that all of its personnel engaged in the service provision shall have the education, training (including GDP training), and experience sufficient to perform their assigned functions. This includes any temporary/contract resource.

3.3 Service Provider shall have facilities and equipment of the required standard in place in order to ensure provision of service according to current GDP standards.

3.4 Service provider shall ensure that each Product is prepared for transport in accordance with Applicable Laws and Regulations and the labelling for such Product such that the quality and integrity of such Product is not compromised during transport. Where required by Contract Giver, specific temperature monitoring devices shall be consigned with each shipment of Product to verify that the required conditions have been complied with.

3.5 Perform and document validation, qualification and calibration, as appropriate for all equipment, facilities, processes, computers, systems, electronic records and cleaning used in the Storage and Handling of each Product in accordance with Applicable Laws and Regulations and the applicable Product Requirements.

3.6 Further clauses – to confirm compliance in the following aspects: environment control/monitoring, housekeeping, specific Responsible Person activities, FIFO/ FEFO requirements, Documentation retention requirements and lead times for access/provision of such documentation to contract Giver, SOP requirements (can include a list of SOPs), Self-Inspection requirements, expectations versus continuous compliance improvement, sub-contractor management/auditing, need for written procedures, QMS expectations, Product security expectations, Safety Health and Environment expectations, waste management.

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4 Receipt, Identification and Inspection of Incoming Products

Example clauses:

4.1 Contract giver shall deliver Product to Service Provider with accompanying documentation showing identity and quantity of the Product in accordance with Applicable Laws and Regulations and Product Requirements.

4.2 Service Provider shall identify and inspect all Products it receives for any damage or evidence of tampering and for the integrity of the seal of the immediate container, if applicable. Any Product container suspected of being tampered with must be segregated and reported to Contract Giver within x hours. Shippers that are partially full are not required to be opened for checking contents.

4.3 Service Provider shall perform receipt checks and disposition decision in their Warehouse Management System according to internal written procedures to include:

4.3.1 General – damage and general condition.

4.3.2 Temperature compliance during transport

4.3.3 Physical delivery of Product matches expected delivery of Product (Product and Product code, quantity and expiry date.)

4.3.4 Products will be stored one batch per one pallet per pallet location.

5 Personnel

Detail in this section, for example,

- Responsible Person (RP) and Deputy RP will be appointed
- Personnel involved in GDP activities have appropriate ability and experience and are periodically trained in GDP and in the procedures that pertain to their job description
- Training records will be maintained

6 Premises/Storage

Detail in this section, for example,

- Premises to ensure proper conservation, security and distribution of products
- Pest control program
- Temperature mapping
- Monitoring and recording of storage conditions
- FEFO (First Expired First Out) stock rotation system
- Separate and segregated area for receipt and storage of rejected goods, returned products and quarantined products

7 Storage of Product

Detail in this section, for example,

- Storage conditions available (e.g. storage under refrigeration (2-8°C), storage less than 25°C, controlled drug storage etc)
- Documentation, investigation and communication of temperature excursions

8 Delivery to Customers

Detail in this section, for example,

- All product is distributed in accordance with GDP
- Distribution only to parties entitled to receive products
- Transport under any special storage conditions required using own vehicles or approved carriers
- Traceability

9 Quality Assurance and Quality Control

Detail in this section, for example,

- Product disposition responsibilities
- Customer verification responsibilities
- Responsibility for attaching temperature monitors, where applicable
- Right for Contract Giver to audit, including notice periods and requirement for contract acceptor to define and deliver CAPA

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- Arrangements for notifying each other of regulatory inspections, and details to be shared, how to deal with actions etc.
- Prohibition of outsourcing activity to 3rd party without Contract Giver approval.
- Any specific activity exclusions (such as product rework)
- Key Performance Indicators, performance review meeting frequency.

10 Deviations and Investigations

Detail in this section, for example,

- How to handle non-conformances/deviations including timescales and documentation requirements.
- CAPA expectations
- Issue Management processes, including references to key contacts in Appendices
- Recall roles and responsibilities, including expected timescales, documentation and product handling expectation.

11 Change Control

Detail in this section, for example,

- Requirement for change management according to a written procedure and including QRM principles
- Expectations to inform the Giver/Acceptor party of changes, and prior approval expectations.

12 Product Quality Complaints/Adverse Events/Counterfeits

Detail in this section, for example,

- Two-way communication expectations in the event of the above, including timing (verbal and written)
- Responsibilities for respective investigations, including documentation and timing.

13 Product Returns and stock adjustments

Detail in this section, for example,

- Responsibilities for management of returns, and requirements for specific checks.
- Responsibilities for disposition decisions, and criteria for accepting material back to saleable stock.
- Any specific "above GDP" requirements – for example a policy of no cold chain returns.
- Stock discrepancy procedures/responsibilities, and what to do in the event of possible product quality impact of a discrepancy.
- Product destruction requirements (Written authorisation may/may not be required from contract Acceptor, Certificate of Destruction, provision of an itemized list to the Contract Acceptor, method of disposal etc.)

14 Product Recall

Detail in this section, for example,

- Responsibilities, timescales and documentation requirements.
- Decision owners
- Communications with regulatory authorities
- Requirements for quarantine, reconciliation reports etc.

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APPENDIX A

RESPONSIBILITIES MATRIX

This matrix is for reference purposes. The full wording of each Article is contained in the main body of the QA Agreement and takes precedence over this matrix wording in the event of any conflict.

RESPONSIBILITY FOR	Contract Acceptor	Contract Giver
INTRODUCTION AND SCOPE		
Include key clauses from main body of the QTA, including item		X
		X
	X	X
GENERAL		
	X	
	X	
RECEIPT, IDENTIFICATION AND INSPECTION OF INCOMING		
		X
	X	
	X	
QUALITY ASSURANCE AND QUALITY CONTROL		
		X
ETC		X

APPENDIX B

SERVICE PROVIDER SITES

This matrix is for reference purposes. The full wording of each Article is contained in the main body of the QA Agreement and takes precedence over this matrix wording in the event of any conflict.

List Sites relevant to service provision

APPENDIX C

PRODUCT LIST AND REQUIREMENTS

List, for example, the products applicable to the service provision, with key information tabulated. Consider product description, codes, storage and shipping temperature requirements, temperature monitoring requirements, and hazardous materials etc – all the information a Contract acceptor might need to execute responsibilities properly.

APPENDIX D

CONTACT NAMES

Contract Giver

Primary Contact	Alternate

Contract Acceptor

Primary Contact	Alternate

APPENDIX E

DEVIATION DEFINITION AND FORM TO REPORT DEVIATIONS TO CONTRACT GIVER

Define here what events should be reported to contract giver, and provide a template for reporting such events.

APPENDIX F

FORM OF CHANGE CONTROL REQUEST

Provide a standard form to Contract Acceptor to inform Contract Giver of proposed changes.

APPENDIX G

GUIDELINES FOR CHANGES REQUIRING COMMUNICATION AND PRIOR APPROVAL

Define here those changes at Service Provider that should be communicated/ approved using the form in appendix F.

Include a list of approved sub-contractors and suppliers, changes to which require prior approval.

APPENDIX H

KEY PERFORMANCE INDICATORS

Define Key Performance Indicators and review processes

e.g.

- number of deviations due to service provider (specify target limit)
- complaints due to service provider (specify target limit)

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APPENDIX I

CHANGE HISTORY

Revision No.	Description of Change	Effective Date

APPENDIX 2:

GOOD AND POOR TRANSPORTATION PRACTICE EXAMPLES

This appendix provides some additional examples of good practices to supplement the guidance in Chapter 9. It also provides some examples of poor practices drawn from audit findings and quality incidents which it is hoped will further illustrate the importance of compliance.

9.1. Principle

Example of good practice – a risk-based approach to planning transportation

Use knowledge of the supply chain to document a risk assessment with appropriate risk mitigation actions. An example is detailed below. Map the supply chain as a precursor to the risk assessment. Note that gaps in knowledge are automatically given a high risk score.

Example scoring table and overall risk rating table (derived from multiplying all individual factors)

Score	Product Storage Condition	External Environment conditions	Storage Risk Rating	Duration of Journey	Vehicles
1	<30°C	Winter (2 - 10°C)	No unapproved/ unaudited hubs	1– 5 hrs	No more than 2 vehicles used for whole chain
2	15°C -25°C	Spring/ Autumn (10 – 20°C)	At least one unapproved/ unaudited hub	5 – 15 hrs	More than 2 vehicles known to be used
3	2°C -8°C	Winter (<0°C and product impacted by freezing) OR Summer (>20°C)	No knowledge of hubs	>15 hrs	No knowledge of vehicles

Overall risk rating

1 - 4	6 - 12	16 - 32	36 - 72	81 - 243
Very Low	Low	Medium	High	Very High

Example Risk Assessment and Risk Mitigation Plan using the scoring table

Risk Assessment

Product	Product Storage Condition	External Environment conditions	Storage Risk Rating	Duration of Journey	Vehicles	Overall shipment risk rating
Example	2°C - 8°C 3	Up to 28°C 3	Unknown 3	12 hours 2	Unknown 3	Very High 162

Risk Mitigation Plan

Although the overall risk rating from this assessment is very high, because the duration of the journey is only 12 hours, use of a qualified 48 hour passive shipper configuration together with monitoring should be appropriate to mitigate the risk.

The supply chain will be audited to eliminate the unknowns regarding the number of hubs and vehicles used.

Technical Agreements will be updated to stipulate greater control.

Following these actions, the risk assessment will be updated. Data from the monitoring of shipments will provide additional input to this updated assessment. Following the updated assessment, the risk score and mitigating actions will be reviewed.

Examples of poor practice

- It is not unusual to find that a Risk Assessment has not been carried out and documented.
- A risk assessment that does not cover the whole shipment chain or is based on assumptions can underestimate the risk and may not result in appropriate mitigation actions being taken.

9.2. Transportation ((i)- Understanding and control of required storage conditions)

Examples of poor practice

- Shipping +15°C to +25°C product in standard shipping container during summer or winter without data loggers.
- Shipping +2°C to +8°C and +15°C to +25°C product in the same temperature compartment on a vehicle to reduce cost. Each should be in their appropriate temperature compartment.
- Product is shipped without labelling specifying product temperature or storage requirements.
- Lack of control throughout the supply chain results in product being left in temporary locations without assurance of storage conditions.

9.2. Transportation ((ii) Control of vehicles)

Examples of good practice

- Use of solid-sided vehicles with secure locking mechanisms and recorded security seals,
- Use of temperature controlled vehicles where appropriate.
- GPS tracking of vehicles provides an additional level of assurance.

Example of poor practice

- Using curtain sided vehicles for high value, temperature sensitive products. Such vehicles cannot control temperature and are vulnerable to theft.

9.2. Transportation ((iii) Dedicated vehicles)

Examples of poor practice

- Shipping medicinal products in non-dedicated vehicles without risk assessment and clear stipulation limiting what other materials may be in the vehicle.
- Medicinal products were shipped in a non-dedicated vehicle in which a strong-smelling chemical was also transported, resulting in them becoming tainted.

9.2. Transportation ((iv) Deliveries and emergencies)

Examples of poor practice

- A medical product delivery was left at the reception desk as the consignee was not available at the time. The receptionist was off duty on that day and no one took notice of the delivery. The supplies had a 2-8°C storage condition and by the time they were in the possession of the consignee they had exceeded the maximum allowable time out of cold storage.
- A lifesaving drug required an emergency delivery which was planned for a Friday at 3.30pm. However, a standard courier was used for the delivery which did not guarantee delivery at the required day/time. The product was not delivered until the Saturday morning and this put the patient at significant risk.

9.2. Transportation ((v) Contractors and temporary storage)

Examples of good practice

- GPS and track-and-trace techniques should be used to manage the movement of products. Devices are now available that can be placed on a pallet or individual box so that the actual location of the product can be known at any point in time.
- Make full use of other available technologies too to minimise potential issues, as in this example: A shipment was collected from a UK wholesaler on a Friday destined to travel by air to France. An airline strike was called which could have significantly impacted the shipment but, through use of web-based systems, the carrier was able to assess the risk and make alternative arrangements to route the shipment by road. This avoided both delay and additional risks that might have arisen from use of temporary storage.

Example of poor practice

- One of the pallets in a five-pallet delivery was as in Figure 9. The clear shrink wrapping should have completely covered pristine white boxes, but in this case the shrink wrapping was extremely dirty and through a tear a footprint was evident on top of a box. On investigation, it was discovered that the pallets had been stored in a temporary storage location for almost two weeks over the Christmas and New Year holiday. Further, this storage location was not approved for use in the Technical Agreement,

did not have regulatory authorisation and was lacking in many basic GDP requirements. Consequently, the whole shipment was rejected.

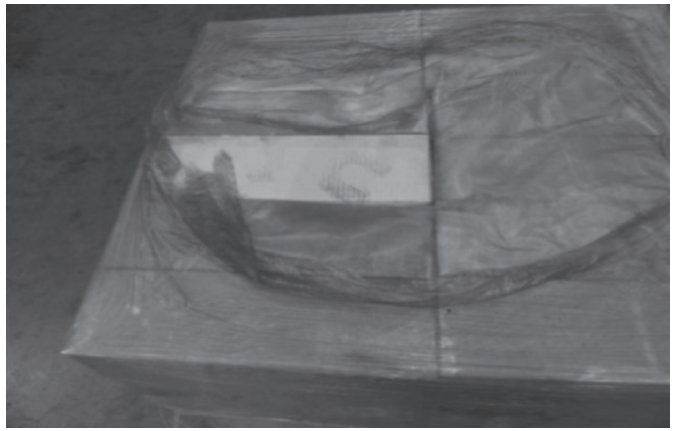

Figure 9: Photograph of unacceptable pallet on receipt

9.3. Containers, packaging and labelling

No additional guidance

9.4. Products requiring special conditions ((i) Safety of narcotics, highly active and radioactive materials)

Example of poor practice

An untrained driver delivered one of these products to the incorrect location on a hospital site. The pharmacy noticed that the product had not arrived as part of the required morning delivery and the supplier was contacted immediately. The signature on the 'proof of delivery' record was unreadable. Thanks to prompt action, a replacement product was successfully delivered that afternoon to enable continuity of patient supplies, but this error could have impacted patient health as well as causing inconvenience.

9.4. Products requiring special conditions ((ii) Temperature sensitive products)

Examples of poor practice

- Changes were made to the packaging of a shipper which was used without further qualification as staff did not think the changes would make any difference. Fortunately, loggers were also used as in this way it was detected that the change had significantly reduced the period over which the intended conditions were maintained.
- A Wholesaler shipped a cold chain product to a customer using a passive shipper. On receipt, the logger data were within the 2 – 8°C storage conditions. However, on opening the container, product was found in a frozen state and had to be rejected. The packaging protocol had not ensured that the ice packs did not come into direct contact with the product or that the logger was exposed to the same conditions as the product.
- A medical product shipment, which was time and temperature sensitive, was stopped at Customs due to the officer requiring further documentation. Customs clearance took longer than had been anticipated as part of the shipper qualification and, as a result, the product was found to be out of storage conditions on arrival.

9.4. Products requiring special conditions ((iii) Temperature controlled vehicles)

Examples of good practice - Additional detailed guidance on the implementation of effective mapping of vehicles

The overall aim is to generate comprehensive documentation of mapping with impact tests and representative loads to provide evidence of how the vehicle operates when challenged in the designated configurations.

- The intended vehicle should be placed 'outside' during mapping activities. Note : large climatic chambers can be used but only simulate artificial rather than real life conditions
- Consideration should be given to the representative load size, footprint and configurations during the mapping. E.g., Testing should simulate Full and Half loads. Empty conditions can also be considered to monitor chiller/control performance.
- If the vehicle has a dual compartment/temperature capability, consideration should be given to mapping all configuration options that will be used.
- Logger placement rationale for the mapping should allow for sufficient coverage of the vehicle, covering each of the upper & lower corners, as well as central locations. When using dummy loads, loggers can be attached directly to the load following a similar pattern.
- 'Lower' locations should be at pallet height (15 to 20cm) and 'Upper' positions should be at the highest point that the product will be placed.
- The vehicle should be marked with load limit lines to avoid product being stacked in ways that compromise air flow.
- If an additional electrical power supply is fitted, e.g., for use on ferry crossings or during overnight stops, then this should be considered during the mapping in addition to running on engine power.

- Consider the air outlet temperature by placing probes to monitor air outlets and inlets.
- Place loggers on the outside of the vehicle to document external temperatures and compare the data to look for any trends between internal and external results.
- Note the locations of the CMPs (Continuous Monitoring Probe) within the vehicle and make a comparison of the vehicle readings to the mapping data. Note CMPs are often placed above the load limit line and are not at product level.
- Consider basic impact tests such as:
  - 'Power-down' tests to document the time period that the chamber maintains temperature in event of power supply failure
  - 'Door open' tests to document changes during the periods of loading and unloading
  - Record the dates and times of start/finish of impact tests and compare to mapping data to assess the impact on environment
  - If using non-controlled vehicles for temperate product, mapping should still be a consideration and part of a documented risk assessment

Examples of poor practice

- Continuing to rely upon devices with a calibration status that has expired (e.g. >12 months)
- Using devices outside of the checked range. e.g. using a device calibrated at 0°C/+5°C /+10°C but in +20°C conditions
- Utilising vehicles that have not been mapped or properly qualified for intended use

9.4. Products requiring special conditions ((iv) Demonstration of control)

Examples of good practice

- Monitoring shipments with data loggers/probes located in load positions that have been justified through mapping data
- For lower risk product shipments, documented justification of the assessment with evidence of 'worst case scenario'

Example of poor practice

- Not having evidence of transit conditions or justification providing assurance of these.

9.4. Products requiring special conditions ((v) Use of cool packs)

Examples of poor practice

Many of these occur because of failure to stipulate and/or follow details in procedures. Examples include:

- Cool packs placed randomly in the freezer.
- Personnel not sure when cool packs were loaded into the freezer/are ready for use
- No processes for ensuring the packs are acclimatised at the correct temperature for the required amount of time (clear signage is required as it is not always easy to visually distinguish partly and fully frozen packs)
- Not preventing the cool packs from coming into direct contact with the product.
- Not packing the insulated boxes in accordance with a validated packing specification
- Reusing damaged components.

9.4. Products requiring special conditions ((vi) Delivery of sensitive products and seasonal variations)

Example of poor practice

On investigating complaints about the efficacy of a batch of inhalers shipped to the Middle East, it was identified that the consignment had been subject to significant day-night temperature cycling (0°C - 40°C). As this had not been anticipated, arrangements had not been made to mitigate the risk through appropriate packaging and monitoring.

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