Good manufacturing practices
for
Active ingredient manufacturers

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EUROPEAN FEDERATION
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1. Acknowledgements

The ad hoc EFPIA / CEFIC Working Group which drew up these guidelines acknowleges the contributions made by the Pharmaceutical Quality Group of the Institute of Quality Assurance and British Quality Association to the advancement of Good Manufacturing Practices for Active Ingredients through the publication of the monograph „Bulk Pharmaceutical Chemicals“ in July 1992.

This ad hoc EFPIA / CEFIC Working Group also acknowleges the previous work of the Bulk Pharmaceutical Chemicals Committee of CEFIC which drew up the original CEFIC GMP guidelines and completed this as far as the Final Draft stage and the work of the ad hoc Working Group of the German Pharmaceutical Research and Manufacturers Association (VFA) which drew up the VFA “Recommendations for Good Manufacturing Practices for Active Ingredients“. These two documents were used as the basis for the present document.

2. Introduction

This introduction reviews the development of Good Manufacturing Practices (GMPs) for Active Ingredients (A.I.s.) and explains the purpose of the present Guideline.

In the USA, although the FDA has not yet issued separate GMP regulations for active ingredients, to assist agency personnel, guidelines have been produced entitled "Guidelines to the Inspection of Bulk Pharmaceutical Chemicals". These were last updated in May 1994.

Guidelines have also been developed in the USA by PhRMA (Pharmaceutical Research Manufacturers Association) entitled "Guidelines for the Production, Packing, Repacking or Holding of Drug Substances" which were published in September 1995.

A WHO guideline for active pharmaceutical ingredients is included in Chapter 18 of the 32nd report of the World Health Association, Geneva, 1992.

In Japan, standards for the Manufacture of BPCs' mainly emphasising responsibilities in active ingredient manufactures.were issued from the Pharmaceutical Affairs Bureau of the Ministry of Health and Welfare in 1988.

In Europe the Pharmaceutical Inspection Convention (PIC) issued a "Guideline for the Manufacture of Active Pharmaceutical Ingredients" in June 1987. This document has not been revised since its original publication and provided the basis for the WHO guide cited above.

In the European Union the principles of GMP for medicinal products were laid down in the "Guide to Good Manufacturing Practice for Medicinal Products" in Volume IV of "The Rules governing Medicinal Products in the European Community". This guide states that, for the manufacture of active ingredients, the PIC document was an appropriate reference. This PIC document therefore is, at present, the only official guidance available to all member states of the European Union.

In several countries manufacturers of active ingredients found that the PIC document did not provide sufficient guidance, and thus several organisations in Europe published more detailed guidelines for GMP of active ingredients. These include the French SICOS Biochimie, the Italian Aschimfarma, the UK Pharmaceutical Quality Group, the "Guidance for Bulk Pharmaceutical Chemical Manufacturers" developed in 1994 by CEFIC (the European Chemical Industry Council) and the German VFA (the Association of Research-based Pharmaceutical Manufacturers) document of February 1995: "Recommendations for Good Manufacturing Practices for Active Ingredient Manufacturers". It is this VFA document that EFPIA, the European Federation of Pharmaceutical Industries Association, adopted as the basis for a European Industry Guideline for Active Ingredients.

The present document has been produced by a joint EFPIA/CEFIC working group and reflects the objectives of both associations to produce and publish one guideline suitable for all active ingredient manufacturers. Its purpose is to serve as a **guide**, with the intention of ensuring that active ingredients are manufactured under a quality assurance system which is appropriate for their subsequent use. The scope is limited to GMPs for active ingredients, excipients are not covered.

3. Scope

The document describes Good Manufacturing Practices for substances intended to be used as therapeutically active ingredients of medicinal products for human use.

NOTE 1 Any substance from organic, inorganic, microbiological, animal or plant origin, or material produced by recombinant DNA methods and purported by the producer to provide therapeutic activity is an Active Ingredient, (A.I.) even if it is not recognized or offered as such in every member state of the European Union.

3.1 Purpose of the recommendations

The following recommendations are intended to serve as a guide for the European active ingredient manufacturing industry with the intention of ensuring that active ingredients are manufactured under a quality assurance system which is appropriate for their subsequent use.

These recommendations are also suitable for use in the inspection of active ingredient manufacturers either through a Self-Inspection programme or by the designated authorities.

3.2 The recommendations and their key concepts

3.2.1 These recommendations are based on the following basic assumptions:

(1) The term Active Ingredient (A.I.) includes all types of active ingredients providing therapeutic activity for human use.
(2) These GMP recommendations should be applied to the production steps of A.I.s as defined below.

3.2.2 These recommendations are appropriate for the manufacture of all types of A.I.s, but different measures may need to be taken in the manufacture of materials and A.I.s from microbiological, animal or plant origin including A.I.s produced by recombinant DNA methods.

3.2.3 These recommendations do not cover the production of sterile A.I.s.

3.3 Application of GMP principles

3.3.1 Full evidence of GMP compliance should be given from that stage in the production of an Active Ingredient where the analytical specifications of the materials alone, together with the subsequent production steps are sufficient to ensure the quality of the A.I. This stage is no later than the step(s) starting with the final intermediate.

A.I.s obtained by extraction should be subjected to GMP principles from the first critical step in the production.

3.3.2 Earlier steps in the production of active ingredients need not be manufactured according to these guidelines, but should be controlled under an appropriate quality system

3.4 Notified information

For many A.I.s various aspects (e.g. source, route of synthesis, control methods, specifications) are likely to have been notified to one or more National Authorities under a Product Licence, New Drug Application, Drug Master File, Marketing Authorization Application or Certificate of Suitability dossier. The manufacturer has a legal obligation to adher to the notified information. When appropriate, changes should be notified to the relevant authorities and users be informed so that actual practice and the notified information are in agreement.

4. Glossary of terms

The definition of terms used in these guidelines follow those given in the European GMP Guide 91/356/EEC or as generally understood by manufacturers of Active Ingredients (A.I.s). Some terms of particular significance in these guidelines are defined below:

Active Ingredient (A.I.)

Any material from organic, inorganic, microbiological, animal or plant origin, including that produced by recombinant DNA methods used in the manufacture of a medicinal product for human use which provides the therapeutic activity.

> NOTE 2 Active ingredients are usually first obtained in the crude state, and subsequent production operations convert the crude A.I. to the pure A.I. which is intended to meet a pharmacopoeia or similar requirements. A final A.I. is a pure A.I. which has been subjected to additional physical processing steps, such as micronizing, milling, or sieving necessary to convert the pure A.I. into a material with the required physical characteristics. The pure A.I. can also be the final A.I. when no further processing steps are necessary.
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> NOTE 3 Other synonyms are Active Substance or Principle, Drug Substance, or Medicinal Substance.

Batch (or lot)

A defined quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production a batch must correspond to a defined fraction of the production, characterised by its intended homogeneity. The batch size may be defined either by a fixed quantity or the amount produced in a fixed time interval.

> NOTE 4 To complete certain stages of manufacture, it may be necessary to divide a batch into a number of sub-batches, which are later brought together to form a homogeneous quantity.

Batch number (or lot number)

A distinctive combination of numbers and/or letters which specifically identifies a batch or lot and from which the production history can be determined.

Calibration

A set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard.

Computer system

A system including the input of data, electronic processing and the output of information to be used either for reporting or automatic control.

Computerized system

A system including computer system, all sensors, transmitters, actuators and wiring needed to control the process.

Contamination

The unintended, non-process related, introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a material during production, sampling, packaging or repackaging, storage or transport.

Continuous production

A process in which a material is continuously produced in a step or series of steps. In a continuous process the batches of raw materials and the process parameters can be statistically, but not absolutely, correlated to the material produced in a given window of time.

Critical

A material (e.g. raw material, packaging material, process aid, intermediate), process step or process condition, test requirement or any other relevant parameter is considered to be critical when non-compliance with predetermined criteria directly influences the quality attributes of the Active Ingredient in a detrimental manner.

Cross contamination

Contamination of a material or product with another material or product, thus cross contamination is a particular form of contamination.

Final intermediate

The last compound from which the Active Ingredient is produced. In the case of organic compounds this means a change in at least one covalent bond whilst for inorganic compounds this may mean a change in an ionic bond. The final intermediate is thus a starting material for the process step which produces the Active Ingredient.

Final production stages

The purification and subsequent process steps to give the pure Active Ingredient and, if necessary, the further steps to produce the final Active Ingredient.

Impurity

Any component present in the active ingredient other than the substance defined as the A.I.

NOTE 5 A contaminant is a particular form of impurity.

In-process control

Checks performed during production in order to monitor and, if necessary, to adjust the process, including repeating a process step, to ensure that the product conforms to its specification. The monitoring of the environment or utilities may also be regarded as a part of in-process control.

Intermediate

Partly processed material which must undergo further production steps before it becomes an Active Ingredient.

Manufacture

All operations of purchase of materials and products, Production, Quality Control, release, storage, distribution of Active Ingredients and the related controls.

Materials

A general term used to denote Raw Materials, Process Aids, Intermediates, Active Ingredients and Packaging Materials.

Packaging materials

Any material used to protect an Active Ingredient during storage and transport but excluding labels.

Procedures

Description of the operations to be carried out, the precautions to be taken, and measures to be applied directly or indirectly related to the manufacture of an Active Ingredient.

Process aids

Materials used as an aid in the manufacture of an Active Ingredient which themselves do not participate in a chemical or biological reaction.

Production

All operations involved in obtaining an Active Ingredient commencing with the receipt and storage of raw materials and continuing through processing to packaging, labelling and storage.

Qualification

The action of proving that any equipment is properly installed, works correctly, and consistently produces the expected results. Qualification is part of, but not limited to, the validation process.

Quality attribute

Any product characteristic which may reflect quality, or may affect safety or efficacy of the product during its expected shelf life.

Quality assurance

It is the sum total of the organised arrangements made with the object of ensuring that Active Ingredients are of the quality required for their intended use.

Quality control

Quality Control is one or more organisational unit(s) with defined responsibilities for controlling, through checking or testing, that specifications are met and quality systems are maintained.

Quarantine

The status of materials isolated physically or by other effective means whilst awaiting a decision on their subsequent use.

Raw material

Any material of defined quality used in the manufacture of an Active Ingredient, but excluding packaging materials or labels.

Recovery

Any treatment of materials by a process intended to make them suitable for further use.

Reprocessing

The treatment of a batch or sub-batch of materials of unacceptable quality by repeating the same process steps from a defined stage of production so that its quality may be made acceptable.

> NOTE 6: The occasional repeating of one or more process steps during manufacture after it was known that the pre-set limits had not been met, or there was an unexpected process problem, is an acceptable part of the process and a rational reaction to the results obtained.

Reworking

The treatment of a batch or sub-batch of materials of unacceptable quality by using a process other than that used to produce the original material so that its quality may be made acceptable.

Validation

Action of proving and documenting that any procedure, process, equipment, activity or system will, with a high degree of assurance, lead to the expected results.

5. Organisation, personnel and training

Principle

The capability and attitude of all staff involved in the manufacture and control of A.I.s has a decisive influence upon the quality of the products.

5.1 Organisation

5.1.1 Senior management should have a formal commitment to compliance with Good Manufacturing Practices.

5.1.2 The organisation should be described in an organisation chart from which it can be seen that Production and Quality Control operate independently from each other.

The key personnel, and their deputies, should be qualified by education, training and experience for their assigned responsibilities. The latter should be laid down in writing.

5.2 General personnel and training

5.2.1 Personnel at all levels should be sufficient in number to carry out their tasks according to the prescribed procedures.

5.2.2 Personnel involved in the production and control of A.I.s should be adequately trained, including training in GMP. Training should be carried out at appropriate intervals and when new processes are being introduced. Training should be given to other personnel whose activities affect critical aspects of production and/or control of A.I.s. Records of training should be maintained.

5.3 Hygiene

5.3.1 Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities which could result in compromising the quality of A.I.s.

5.3.2 Personnel should avoid direct contact with A.I.s.

5.3.3 Personnel should wear clothing suitable for that type of manufacturing activity they are involved in. Such clothing should be designed to protect both product and personnel and should be worn by all involved in the manufacture of A.I.s. Clothing and appropriate safety and protective garments should be changed when necessary.

6. Facilities and utilities

Principle

Buildings should be of adequate size and should be located, designed, constructed, adapted and maintained to suit the operations carried out in them. Adequate utilities should be available and suitable areas for the manufacture, testing, and storage of A.I.s should be provided.

6.1 Buildings

6.1.1 Buildings should be designed, located, and constructed or adapted so that they are suitable for the type and stage of manufacture involved.

6.1.2 Where the equipment itself affords adequate protection for the product, such equipment may be located in the open air if so desired.

6.1.3 The construction of buildings should facilitate easy cleaning, and minimise the accumulation of water.

6.1.4 The handling of pure and final A.I.s should be carried out in an environment giving adequate protection against particulate- and, if necessary microbiogical- as well as (cross)- contamination.

6.1.5 Separate production areas and equipment should be used for the production of sensitising A.I.s such as penicillins and cephalosporins.

6.1.6 Other A.I.s of high activity or toxicity, such as certain steroids, cytostatic substances etc. may require separate production areas and equipment.

6.1.7 Facilities for changing clothes, washing, toilets, rest and refreshment rooms should be available and separate from the production areas.

6.1.8 Laboratory areas for final product testing should normally be separated from production areas. Such a separation is essential when the side-effects of the production process such as vibration etc. could affect the accuracy of the laboratory measurements.

6.2 Ventilation

6.2.1 Ventilation systems, where necessary, should be designed and constructed so as to protect both the operators and the A.I.s.

6.2.2 Filters in ventilation systems should be capable of sufficiently removing particulate contamination down to a defined level.

6.2.3 Recirculated air should not cause cross contamination.

6.2.4 Air intake points should be adequately separated from potential sources of contamination such as air exhaust points.

6.3 Utilities and services

6.3.1 All general utilities should meet specifications appropriate for their intended use.

6.3.2 Critical utilities should be regularly monitored to ensure that specifications are met and action is taken when warning limits are exceeded.

6.3.3 Water

The quality of the water used in the manufacture of an A.I. will depend on the product and processing stage; in many cases potable water is quite suitable but, for certain processes it may be necesary to remove excessive ions, to reduce the microbial load and/or remove endotoxins. Appropriate specifications for the chemical and microbiological quality of each type of water should be established. Water meeting different quality standards at an A.I. manufacturer should be named differently. Typical examples of the types of water that could be used in an A.I. plant are given below.

6.3.3.1 Potable water

The source of such water will normally be water of potable quality from a defined source, however care must be taken to ensure that local or national regulations regarding connections to the plant water system are met to prevent back flushing.

> NOTE 7 The break from the mains supply can results in loss of microbial control so that measures may need to be taken to maintain the system under control. Such measures might include adding antimicrobial agents, regularly sanitizing or disinfecting the system or other measures which are designed to keep the microbial load below a specified level if this is essential to achieve product quality.

6.3.3.2 Treated water

Treated water is potable water or other source water which has been suitably treated to meet the approved chemical and microbiological specifications.

> NOTE 8 Methods of treatment could include, (but not necessarily be limited to one of these alone): filtration, deionization, ultra- filtration, reverse osmosis or distillation. Such water is often refered to as Purified Water, Demineralized
>
> Water, Softened Water, or Deionized Water, etc. If not carefully controlled, it may not routinely meet the applicable microbiological specifications, and thus

measures may need to be taken to maintain the specification, as outline in Note 7 above.

6.3.3.3 Endotoxin-free water

Endotoxin-free water is water which has been treated to reduce the quantity of CFUs and endotoxins to below a specified level.

NOTE 9 The methods of treatment which provide the necessary endotoxin and CFU reduction include purpose filtration, ultrafiltration, reverse osmosis or distillation.

6.3.3.4 Heating or cooling water

Water which is in use in the plant for heating or cooling purposes will generally be of lower quality than the types of water mentioned above; however care must be taken to prevent such water from contaminating materials or equipment in direct contact with A.I.s.

6.3.4 Steam

The quality of steam used for indirect heating is generally not critical for product quality, however if steam is injected directly into the process it should meet an appropriate and approved specification which generally will limit noxious boiler additives which could affect product quality.

6.3.5 Other utilities

If other utilities are critical for the operation of the process it may be necessary to establish specifications for these.

6.4 Pipework

6.4.1 Utilities should be supplied to the points of use using pipeworking and valves designed to minimise the risk of contamination of both the utility and the A.I.s or their intermediates.

6.4.2 Permanently installed pipework should be labelled with the name of the material therein and indicate the direction of flow. Such pipework should be so located that rust, condensate on the surfaces, or leakages will not result in the contamination of any critical material or A.I.

6.5 Waste disposal

6.5.1 Containers for waste material should be clearly identified as such.

6.5.2 All disposal of solid, liquid or gaseous by-products from manufacturing should comply with the locally applicable environmental protection laws.

6.6 Security

6.6.1 There should be a plant security system in operation to prevent unauthorized persons gaining access to A.I. manufacturing facilities. Additional security precautions may be necessary if certain types of A.I.s are manufactured, e.g. controlled substances.

6.7 Storage facilities

6.7.1 Facilities should be available for the storage of raw materials, intermediates, A.I.s and packaging materials under appropriate conditions. Records should be maintained of these conditions if they are critical for the maintenance of product characteristics.

6.7.2 Certain materials may need to be stored in the open. In such cases additional precautions should be taken to avoid the loss of markings such as name, batch number, or status.

6.7.3 Unless there is an alternative system to prevent the unintentional or unauthorised use of rejected, returned, or recalled materials, separate storage areas should usually be assigned for their temporary storage until the decision as to their future use has been taken.

6.8 Cleanliness and hygiene

6.8.1 Facilities used to store, produce or control raw materials, intermediates, A.I.s and packaging materials should be kept clean and tidy.

6.8.2 Smoking, eating, or drinking and the storage of food should be restricted to certain designated areas separate from the production or control areas.

6.8.3 Cleaning of premises should be carried out according to written procedures and should generally prohibit the use of compressed air. When sanitization or disinfection is necessary the procedures should specify the agent to be used and the period of usage.

7. Equipment and production

Principle

Equipment and processes will vary widely depending on the A.I. being produced and the scale and type of process operation. As, in general, equipment and processes employed are those of the chemical industry rather than the pharmaceutical industry, closed systems are used, which provides protection against contamination. However particular care needs to be taken after the pure A.I. has been obtained.

7.1 Equipment

7.1.1 Equipment used in the manufacture of A.I.s should be designed, constructed and located so as to minimise the risk of contamination or mix-ups during the manufacture of A.I.s.

7.1.2 Equipment should be non-reactive with respect to the materials contained therein. Food grade lubricants and oils should be used whenever there is a risk of contamination of A.I.s.

7.1.3 Closed equipment should be used when feasible. When open equipment is used, or equipment is opened, care must be taken to avoid contamination of the products within the equipment, particularly when such products are pure or final A.I.s.

7.1.4 The equipment to be used should be suitable for its intended purpose and if the reproducible performance of the equipment is critical for maintaining product quality, the equipment should have been qualified.

7.1.5 Equipment should be clearly labelled and its status identifiable at all times.

7.2 Cleanliness of equipment

7.2.1 Product contact surfaces of equipment, and the connections between equipment, should be easily cleanable.

7.2.2 Procedures used to clean equipment, including related equipment such as heat exchangers and the connections between equipment, should be laid down in writing. Equipment or connections which are difficult to clean in situ may need to be dismantled. Records should be made that the equipment was cleaned as directed, and the cleanliness status of the equipment should be apparent.

7.2.3 Cleaned equipment should be kept closed wherever possible or otherwise protected from recontamination. Equipment should be checked that it is clean before use, and this check should be recorded.

7.2.4 The acceptable level of cleanliness obtained from a cleaning method or procedure should be predetermined and based on sound scientific evidence. Analytical testing, such as determining the quantity of residue remaining in the cleaning solvent, should be used to measure the level of cleanliness obtained at least until the cleaning procedure is validated.

7.2.5 Clean-up between successive batches of the same A.I. is not normally required, however the equipment should be cleaned at appropriate intervals and when there is a risk of contamination due to non- acceptable material build-up, microbial growth, or decrease in equipment performance.

7.3 Control of product contamination

Principle

Although contamination and/or cross contamination can occur at any stage of the production of A.I.s, under normal circumstances such potential risks are less important during the early stages of production. However, at the final production stages for the pure and final A.I., measures should be taken to avoid contamination and/or cross contamination of the A.I.

7.3.1 Final production stages for the pure and the final A.I.

7.3.1.1 After the final filtration of the last solution of the pure A.I., or of the pure A.I. itself, appropriate measures should be taken to avoid particulate and/or cross contamination of the A.I. at this and in subsequent processing steps such as isolation, drying, milling, micronizing, or sieving etc.

7.3.1.2 Such measures should include
- the use of equipment designed to minimise particulate contamination,
- the location of such equipment in an environment designed to prevent contamination and specifically cross contamination with other A.I.s,
- the avoidance of contamination due to the use of inadequately cleaned or maintained equipment, corrosion or bearing leakage,
- the use of adequately purified solvents,
- the prevention of contamination through materials or utilities (e.g. compressed air) which have direct contact with the pure or final A.I.s.

7.3.2 Isolation, drying and blending of pure and final A.I.s

7.3.2.1 In addition to the measures mentioned under 5.3.1 special care needs to be taken when isolating and drying the pure or final A.I. due to the contamination risks associated with dry products.

In particular :
- isolation and drying should be carried out in closed systems wherever possible,
- when product must be charged into, or removed from, equipment in the open, special care should be taken to avoid contaminating either other equipment, other products or the environment,
- if local dust extraction alone is used, a subsequent clean-up should be carried out to minimise the risk of contamination or cross contamination.

7.3.2.2 Isolation, drying and blending of highly active or highly toxic A.I.s should be carried out either in closed systems or in separate areas.

7.3.2.3. Selective blending of out of specification A.I.s with quantities of material meeting specification with the intention of disguising defects and producing a product apparently meeting specification is not an acceptable practice. However the blending of plant or animal extracts meeting an IPC limit to meet a subsequent specification is permitted.

7.4 Control, monitoring and testing equipment

7.4.1 Control, monitoring and testing equipment that is important for product quality should be well maintained and calibrated at appropriate intervals. Records of maintenance and calibration should be made and retained.

7.4.2 Critical deviations from approved standards of maintenance and calibration should be investigated to determine if these could have had an impact upon product quality.

8. Computerized systems

Principle

A computerized system should offer at least the same degree of security as a manual system and the validation should be appropriate. The use of computerized systems in the manufacture of A.I.s will vary significantly with the type of process being carried out, but when product quality relies on the correct and reproducible operations of a computerized system, it is expected that there will be documented evidence that the system has been validated for the proposed use and is performing in a reproducible manner.

8.1 Validation

8.1.1 The extent of validation will depend on a number of factors including the use to which the system is to be put, whether the validation is prospective or retrospective and whether or not novel elements are incorporated.

8.1.2 Where a new system is installed, or an existing system is subject to major up-dating, a prospective validation should be carried out. This should include approval of the design and specification, a description of the interaction between the system and the process, the programme and its testing, and the final acceptance for use.

8.1.3 If an existing system was not validated at time of installation a retrospective validation should be carried out. This should include a description of the system covering the principles, objectives, security measures, the scope of the system, how it is used, what shortcomings have not been eliminated and how it interacts with other systems and processes.

8.2 Software

The need to validate software depends on the category of software involved. System-operating and executive software that is tried and tested does not need to be validated. Configurable or specific applications software should be validated. A detailed description of the programme, and a flow chart of all main and sub-programmes showing the interactions should be available.

8.3 Changes

8.3.1 Alterations or modifications to a computerized system should be approved in advance, be subject to the company "Changes Control Procedure", (See Chapter 9), be carried out by authorized and competent persons, and the changes well documented. Evidence should be retained that, after the change, the system performs as intended.

8.3.2 Should it be necessary to temporarily modify or manually override system parameters, the new parameters, including when they were used, should be recorded and retained.

8.4 Testing

Testing and approving computerized systems should not be limited to the computer system but should take into account the way in which the system could impact product quality. Such activities should be well documented.

8.5 Security

8.5.1 The system should, where necessary, identify the persons entering or confirming critical data. Computer systems should be provided with facilities to prevent unauthorized entries or changes to existing entries in the system. A data trail system can be used to document entry or changes.

8.5.2 Where critical data are being entered manually there should be an additional check on the accuracy of the entry. This may be done by a second operator or by the system itself.

8.5.3 If system breakdowns or failures would result in the permanent loss of critical records then a back-up system should be provided. If no reliable electronic back-up system is available, hard-copies should be made and retained according to the requirements given in Appendix I.

8.6 Documentation

Written Standard Operating Procedures should be available but not limited to procedures
- for operating the system(s),
- to be followed in cases of malfunctioning,
- for detecting and recording errors and enabling corrections to be made,
- for restarting and data recovery,
- authorising and carrying out changes,
- for recording changes,
- for electronic signatures.

8.7 Ancillary Aspects

Incidents which could affect the quality of A.I.s or the reliability of records or test results should be recorded and investigated.

9. Documentation

Principle

A good documentation system is an essential element of GMP for the manufacture of A.I.s. A systematic and well designed documentation system not only contributes to reproducible product quality but assists in investigations into product and process deviations and minimises errors due to verbal instructions or lack of records. In automated plants some or all of the required documentation, such as the manufacturing instructions, may not exist as separate text documents, but may be integrated into the programming code of the operating system.

9.1 General considerations

9.1.1 All documents used in the manufacture of A.I.s should be carefully prepared, reviewed, and distributed. They should have an unambiguous title, refer to a specific product or activity when appropriate, be clearly laid out and easily readable.

9.1.2 Documents should be drawn up by persons with knowledge of the process or controls and approved, signed and dated by authorised persons. The validity of documents should be indicated at least by a date, and a version number is also valuable.

9.1.3 All documents should be drawn up and maintained in compliance with any commitment made to any regulatory authority (or similar legal commitments) e.g. in connection with a Product License, NDA/ANDA, or DMF, Ph Eur Certificate of Suitability, etc.

9.1.4 When entries need to be made in documents, sufficient space should be available for the entry, the type of entry, e.g the units used; the person making the entry should be identifiable.

9.1.5 Manual entries in documents should generally be made directly after performing the activity, be legible and indelible. Corrections to entries should be dated and initialled, and explained where necessary. The original entry should still be legible.

9.2 Specifications and test procedures

Principle

Specifications describe the requirements to which materials should conform. It is usual to describe the material and list the properties to be measured together with the limits which are acceptable to comply with the quality attributes. Specifications should finally be approved by a designated person from Quality Control. There should be details of, or reference to the test procedure(s) to be used.

9.2.1 Specifications should be available for raw materials, intermediates where necessary, A.I.s and packaging materials. In addition specifications may be required for certain other materials such as process aids, filters, gaskets or other materials used during the production of A.I.s that could critically impact on product quality.

9.2.2 Written, approved and dated test procedures should be available for checking if the specifications are met. There should be sufficient detail given that a trained worker can follow the procedure.

9.2.3 Test procedures which are critical for measuring product quality should be validated. Published official test procedures, such as in pharmacopoeias or J Assoc.Off.Anal.
Chem. are already validated, but their suitability should be verified under actual conditions of use.

9.3 Test records

Principle

Records of tests carried out should be so documented that these can be easily compared with the specification to ensure that all the necessary tests have been carried out.

9.3.1 Records of tests, should include:
- the name and batch number of the material being tested,
- reference to the relevant specification and the test procedure used,
- an identification of the standard when used,
- any weighing, measurements or reading carried out,
- any observations and calculations and the results obtained,

and should be dated and signed by the person conducting the test.

9.3.2 Records of tests should be independently checked for accuracy, and critical records countersigned when manual calculations are carried out.

9.3.3 Records of tests including charts generated by instruments should be adequately identified and retained so that, when required, they can be used for evaluating final product quality. Retention periods are outlined in Appendix I.

9.4 Production documentation

Principle

Documentation used in production should include written instructions for producing batches of each material, given with sufficient detail that the operators can clearly follow these, and make the necessary records where required, (Batch Production Records). Other documentation used in production should include written instructions for carrying out other necessary activities.

9.4.1 A production overview should be available in writing and should include where applicable, raw materials, reactions, process steps, in-process controls, intermediates, isolation of crude and pure A.I.s and any subsequent steps taken to make these fit for use, e.g. drying, sieving, milling, micronizing etc. Applicable specifications should be included or referenced.

9.4.2 Instructions to produce a batch should be available for each batch size of each product to be produced, and should include, but not necessarily be limited to, specific batch parameters such as quantities of raw materials to be used, the specific equipment required, process steps and process conditions including permitted ranges, and any special precautions which need to be observed.

9.4.3 Instructions for packaging or repackaging a pure or final A.I. should be available and should include, but not necessarily limited to, the designation of the packaging material with direct product contact, any other packaging materials, the labels to be used, and any special precautions which need to be taken.

9.4.4 Instructions for other activities, such as cleaning, calibration, maintenance, etc, should also be available in writing.

9.4.5 A record of each batch of material produced (Batch Production Record, BPR) should be made and include at least the following:
- the name of the material produced and the batch number,
- the date(s) between which the batch was produced,
- the names, batch numbers and quantities of materials used,
- the equipment and
- the process conditions actually used,
- the results of in-process control tests,
- the yield obtained,

and a cross reference to the process instructions being followed if these are not apparent from the BPR. The entries should be made at the time the action is taken. The operator making the entry should be identified, and the person supervising certain operations specified in the instructions should countersign where called for. The entries should be supported by charts and print-outs where critical process steps are being recorded unless other measures adequately document such steps.

NOTE 10 In batch processes with a known product history it may also be useful to calculate the percentage yield with respect to the expected yield, and compare this with ranges determined from previous product history as a method of monitoring the process.

9.4.6 The entire BPR may be created and stored electronically as long as provisions are made for creating a hard copy when necessary.

9.4.7 All deviations from the production instructions should be recorded in the corresponding batch records and should be evaluated by production.

9.4.8 A record of the packaging or repackaging of each batch, unless this is included in the Batch Production Record, should be made and include designation of the packaging materials and labels used.

9.4.9 The completed Batch Production Records should be reviewed by Production for completeness and consistancy and signed off by the responsible person in Production management. Retention periods are given in Appendix I.

9.4.10 Records of other necessary activities, such as calibration, equipment cleaning on change of product, major equipment changes and repairs, qualification and process validation should be made and retained as given in Appendix I.

10. Validation

Principle

Processes used in the production of A.I.s should be well controlled and critical steps, at least from the final intermediate, should be validated. During early development such validation will normally consists of more intensive in-process and final product control, but for products in the latter stages of development and for commercial products, validation means that there should be written evidence available that the process being used will reproducibly lead to a product meeting its established specification. Facilities, utilities and systems may need to be qualified.

10.1 Validation policy

There should be a written procedure which lays down the circumstances under which validation needs to be carried out, who is responsible for ensuring that processes or methods are validated, and how validation should be conducted and documented.

10.2 Preliminary considerations

10.2.1 Process validation of an A.I. generally starts during the development stage when the critical steps, parameters and process ranges are identified and evaluated. Information obtained during scale-up activities should be used to confirm and refine this evaluation. Manufacture of production scale batches generally provides the evidence that the process is reproducible.

> NOTE 11 Repeated rejection of production scale batches indicates that the process is not under control and thus not adequately validated. The cause for the rejection should be eliminated before any effort is made to revalidate the process.

10.2.2 Before commencing a process validation study on production scale, at least the following points should have been reviewed:

- the facilities, equipment, utilities and systems should meet the requirements for the process and should have been qualified where appropriate,
- the instruments used to measure or control critical parameters should have been calibrated,
- there is adequate evidence that the process, when maintained within the specified limits, will perform as intended in the equipment selected.

In addition

- an approved product specification,
- test procedures, validated where appropriate, and
- a final draft of the Batch Production Record (BPR)

to be used should be available.

10.3 Qualification

10.3.1 When new equipment is installed or existing equipment or utility systems are substantially modified, qualification or re-qualification should be carried out when the equipment or utilities are critical for product quality.

10.3.2 It may be convenient to divide qualification activities into four sub-activities:

- Design qualification (DQ) in which the proposed design of the facilities, equipment or systems is documented as being suitable for the intended purpose;
- Installation qualification (IQ) in which evidence is gathered and recorded that the facilities, equipment or systems as installed or modified, comply with the approved design and the manufacturers recommendations;
- Operational qualification (OQ) in which evidence is gathered and recorded that the facilities, equipment or systems as installed or modified, perform as intended throughout the anticipated operating ranges.
- Performance Qualification (PQ) in which the performance is verified, however in many cases this can be integrated into the process validation activities.

10.4 Process validation

10.4.1 Prospective validation

10.4.1.1 Prospective validation is establishing documented evidence that a system does what it purports to do prior to the commercial distribution of a new A.I. or an A.I. made by a new or modified process.

10.4.1.2 The number of batches to be run will depend on the process and the number of critical parameters but in general three successful sequential runs at production scale under the defined process conditions should be made.

> NOTE 12 For processes or products that are run infrequently this principle cannot always be followed, and it is acceptable to approve such products or processes based on more thorough monitoring and testing of a less than three batches provided this is justified and the justification recorded.

10.4.2 Retrospective validation

Retrospective validation is establishing documented evidence that a system does what it purports to do based on a review and analysis of historic information. It is normally conducted on an A.I. already being commercially distributed, and is based on accumulated production, testing and control data.

NOTE 13 Although less detailed data is usually available, as usually less samples were collected during the process, this lack of data is compensated for by analysing the data from more batches. Analysis of retrospective data may indicate that the process is not under control and a prospective or concurrent validation may then be necessary.

10.4.3 Concurrent validation

Concurrent validation is establishing documented evidence that a system does what it purports to do based on information generated during the actual implementation of the system. It is conducted on an A.I. which will be commercially distributed prior to the completion of the full process validation. Concurrent validation is thus a particular form of prospective validation, in which the batch or batches produced are released, based on more extensive testing, before the entire validation study is complete.

10.5 Scope

10.5.1 It is expected that, at least, the critical steps from the final intermediate will be validated.

NOTE 14 Whilst all steps in the production of an A.I. should be appropriately controlled, it is not necessary to validate every step.

10.5.2 It is necessary to have identified during the development stage the critical process parameters, and defined the ranges necessary for the reproducible operation of the process. In addition the process may require that other parameters be controlled, but such non-critical process parameters need not be included in the process validation studies.

10.5.3 The critical quality attributes of an A.I. should also have been determined during the development phase. Such quality attributes should include, but not necessarily be limited to

- assay, activity or potency,
- qualitative and/or quantitative impurity profile,
- physical characteristics,
- loss on drying and/or,
- residues such as moisture and/or solvents,
- batch homogeneity criteria,
- microbiological attributes where appropriate.

In addition, physical characteristics may also need to have been determined if they are critical quality attributes.

10.5.4 The effect of the following variables upon the process to be validated should be considered
- the facilities in which the process is performed, including, if appropriate, the environmental conditions;
- the equipment and the system in which the process will be conducted, including the control and monitoring devices;
- the process itself, which should be set out in a simple flowsheet and include identification of the process controls necessary;
- the instrumentation which is essential to ensure that the process will perform as designed;
- the training of the personnel including unusual or highly specialized training which might be required in the process.

10.6 Validation documentation

10.6.1 Validation plan

Before commencing validation work a Validation Plan should be drawn up, defining the objectives, the process to be validated, the facilities, equipment, utilities and systems to used, the acceptance criteria, the persons responsible for conducting the work, the persons responsible for reviewing and approving the plan and subsequently reviewing the results. Such a plan should be approved by at least Production and Quality Control.

10.6.2 Validation work

During the conduct of the validation study, data will be collected as specified in the validation plan. Such data should be treated in accordance with the principles of Chapter 7, Documentation.

10.6.3 Deviation review

10.6.3.1 If, during the equipment qualification or process validation work, any run fails to meet the acceptance criteria, then this run should be carefully reviewed to determine the cause for the deviation. This review should be documented. If this deviation can be clearly assigned to a malfunctioning of the equipment or an error on the part of the operator it is permitted to eliminate the run and conduct a new run. However a deviant run may continue to be used in the evaluation, if an explanation of the effect of the deviation is given.

10.6.3.2 If the cause for the deviation cannot clearly be assigned to equipment malfunctioning or operator error, then the materials and/or the process itself should be thoroughly reviewed to determine whether all critical parameters have been correctly identified.

10.6.4 Validation report

On completion of the validation work a Validation Report, cross-referencing the Validation Plan, should be drawn up, summarizing the results obtained, commenting on any deviations observed, and drawing the necessary conclusions. Should the results of the validation not provide sufficient evidence that the process is valid then the report should propose changes which should be made to the facilities, equipment, utilities or process to correct the noted deficiencies. Such a report should be approved by at least Production and Quality Control.

10.6.5 Archiving validation data

The results of validation studies should be readily available when reviewing product history.

10.7 Re-validation

10.7.1 Changes to a validated process, including a number of minor changes, should be reviewed to determine the overall need for revalidation.

10.7.2 Processes should be periodically evaluated to verify that they are still operating in a valid manner. Where no significant changes have been made to the process, a Quality Review as described in Section 15.1, with evidence that the process is consistently producing product meeting its specification, fulfills the requirement for revalidation.

11. Change control

Principle

Changes to manufacturing processes for A.I.s can affect the quality of medicinal products manufactured from such changed A.I.s. A.I. producers should therefore have a system in place to evaluate and approve changes and notify, when appropriate, not only the authorities, but also the user. The amount of information to be forwarded to the authorities and/or the user, if any, will depend on the significance of the change.

11.1 Change control procedures

11.1.1 There should be a written procedures in place to evaluate and approve proposed changes to specifications, test procedures, production processes and production equipment.

11.1.2 As part of the evaluation process the following aspects relating to any proposed change should be considered:
- the significance of the change,
- the potential effect on the quality of the A.I.,
- the potential impact upon the dosage forms which could be manufactured from the A.I.,
- the need to obtain approval from or notify the change to the authorities,
- the need to inform users of the material, and
- the need to revalidate the process.

> NOTE 15 The A.I. manufacturer should be aware that all changes, especially in the final stages of A.I. production, could affect the impurity profile, crystal form, particle size, residual solvents or stability of the A.I., and thus can have a significant impact upon the dosage forms produced from that A.I. Proposed changes should therefore be carefully reviewed before implementing these.

11.1.3 Approval of proposed changes should include approval at least by Production and Quality Control.

11.2 Implementation of changes

11.2.1 When implementing approved changes, measures should be taken to ensure that all the documents affected by changes are revised where necessary.

11.2.2 After the change has been effected, there should be a careful evaluation of the first batches produced under the change.

12. Contract manufacture or analysis

Principle

Production or analysis under contract of those steps of a A.I. process which fall under GMP should also be carried out at the contractor under GMP.

12.1 Contract

12.1.1 There should be a written and approved contract between the contract giver and the contract acceptor, which lays down the responsibilities of each party.

12.1.2 In general the recommendations on GMP as described in these guidelines are also applicable to contract acceptors.

13. Materials management

Principle

Although most processes used in the production of A.I.s are robust enough to cope with variations in the raw materials used, this should not be assumed. It is therefore necessary to ensure that there is an adequate system in place for dealing with raw materials particularly when changes in these are made. The closer the raw material is to the A.I. the more important it is to adequately control the material. Materials used in the production of A.I.s should be purchased against an approved specification. A programme to evaluate suppliers can supplement purchasing against a specification. Changes in the supplier may need to be evaluated for the effect upon the production and/or control of A.I.s.

13.1 Purchasing and control

13.1.1 Raw materials should be purchased against an agreed specification from an approved supplier or suppliers. The specifications should reflect the ability of the process to remove undesirable impurities and include the knowledge gained during process development as to critical properties of the raw materials.

13.1.2 If there is adequate evidence that the supplier can reproducibly provide material meeting the specification, such evidence, such as past quality history, may be used to reduce the amount of in-house testing carried out on raw materials by using Certificates of Analysis from the supplier. However, as a minimum, the identity of each batch of raw materials should be confirmed.

13.1.3 Manufacturers of A.I.s should have a system for evaluating the suppliers of critical raw materials.

13.1.4 Changing the source of supply of critical raw materials should be treated according to Chapter 9, Change Control.

13.2 Receipt and quarantine of materials

13.2.1 Written procedures should be available for checking materials and packaging materials on receipt for correctness of the delivery, for the correspondence between the order and the delivery, the labels and damage to the container or broken seals, tampering, and general suitability for the intended use. Such procedures should include dealing with deviations from acceptance standards when these are detected.

13.2.2 Solvents used in the production of A.I.s should be treated as materials.

13.2.3 If bulk deliveries are made in non-dedicated tank trucks, then there should be written confirmation from the transportation company that cleaning of the tank was carried out before loading the material.

13.2.4 If a delivery consists of more than one lot from the supplier, each lot should be assigned a separate batch or receipt number.

13.2.5 Written procedures should be available to ensure that materials are quarantined until a decision as to their use has been made. Either physical separation or organisational arrangements, including the use of computerized systems, may be used in a quarantine system.

13.2.6 Before incoming materials are mixed with existing stocks, e.g. solvents or stocks in silos, such materials should have been released and procedures should be available to prevent discharging into the wrong stock.

13.2.7 Raw materials susceptable to change with time, e.g hygroscopic or unstable materials, should be allocated a retest period. If such materials are to be used after this period, an evaluation of their properties against the proposed use should be carried out by Quality Control.

13.2.8 Secure storage should be available for printed labels to prevent intermingling.

13.2.9 Rejected materials should be physically separated from all other materials unless there is an equally effective system to prevent the use of such material.

13.3 Issuing or distribution of materials

13.3.1 Materials should not normally be issued for use until the appropriate testing has been completed and the results evaluated against the specification by Quality Control.

13.3.2 Should it be necessary to use materials before evaluation is complete, procedures should be available to ensure that A.I.s manufactured from such materials are not released until evaluation has been completed. At least an identity check should be carried out before using such materials.

13.3.3 If materials are weighed or sub-divided before use, such activities should be carried out in an area designed to minimise the risk of cross contamination.

13.4 Specific management of A.I.s.

13.4.1 Finished A.I.s should be stored under conditions determined to be appropriate to ensure their quality. If the storage conditions are different from room temperature these should be in compliance with those stated on the label.

13.4.2 In addition to the measures applicable to all materials, written procedures should be available to ensure that A.I.s are not released for distribution to third parties before the evaluation by Quality Control has been completed.

13.4.3 Records of the distribution of batches of A.I.s should be so maintained that if necessary the users can be easily contacted, e.g. in the event of a recall.

14. Sampling

Principle

Samples must be truely representative of the batch of material they are taken from. Care must be taken neither to contaminate the sample or the material itself during the sampling process. Particular attention needs to be paid to the facilities used to sample A.I.s.

14.1 Facilities for sampling

14.1.1 Facilities used to sample raw materials should meet the criteria given in Sections 4.1 and 4.8.

14.1.2 Facilities used to sample A.I. should, in addition to meeting the criteria given in Sections 4.1 and 4.8, meet the applicable criteria of Section 5.3.

14.2 Sampling procedures

14.2.1 Sampling tools and containers should be clean and not contaminate either the sample or the product being sampled.

14.2.2 Sampling of materials, when required, should be carried out according to written procedures. Special care should be taken when sampling sensitizing or highly active materials.

14.2.3 Due to their hazardous nature it is sometimes advisable not to open or sample certain materials. In such cases, systems and procedures should be available to ensure that such materials are still fit for use, e.g. by a Certificate of Analysis.

14.2.4 Containers from which samples are withdrawn should be opened carefully, and subsequently resealed. They should be marked to indicate that a sample has been taken.

14.2.5 There should be procedures laying down the number of samples to be taken in relationship to the size of the delivery batch and whether individual or mixed samples should be prepared.

14.2.6 Sampling plans should also be available for primary packaging materials.

14.2.7 When it is necessary to sample containers of A.I.s care should be taken that
- the containers are cleaned before opening,
- the sampling is carried out in an area designed to prevent contamination,
- all containers are resealed in the approved manner, and
- a record is maintained of which containers were sampled.

15. Filling and labelling of A.I.s

Principle

The suitability of A.I.s for their subsequent use depends not only on the production process but also on the protection of the final A.I. from contamination or degradation before use. Care should be taken in the choice of container, and, as the filling of solid A.I.s is often a dusty operation, how this is filled and closed will affect the quality. Labelling, storage and distribution contribute materially to final suitability for use in the manufacture of medicinal products.

15.1 Packaging materials

15.1.2 Evidence should be available that packing materials in direct contact with A.I.s have no adverse effect on the quality of the A.I.s.

15.2 Filling/Packaging

15.2.1 The environment in which the final A.I. is filled into the container, or refilled into other containers, should comply with the requirements of Sections 4.1, 4.8 and 5.3.

15.2.2 A.I.s should be filled so that cross contamination is avoided as far as possible.

15.2.3 Directions for filling an A.I. should include the precautions to be taken, the packaging materials and labels to be used and what checks need to be carried out and recorded.

15.2.4 If reusable containers are used, procedures should be in place to ensure that such containers are appropriately cleaned and checked before being reused.

15.3 Labels and labelling

15.3.1 Control should be exercised over labels used during the manufacture and filling of A.I.s, including label-accountability, to absolutely minimise the risk of label mix-ups or the use of incorrect or out-of-date labels.

15.3.2 Containers of A.I.s should be adequately labelled to meet user requirements as well as compliance with applicable safety and transport regulations.

15.3.3 If the A.I. requires special transport or storage conditions these should be stated on the label and complied with.

15.3.4 Other containers used in A.I. production should be so labelled that the contents are clearly identifiable.

15.3.5 Before reusable containers are used, checks should be carried out to ensure that previously used labels have been removed or defaced.

16. Engineering

Principle

The engineering function has an involvement in compliance with GMP, the extent of which will vary with the responsibilities of the personnel. Systems should be in place to ensure that engineering support of the production and packaging process is timely, adequate, and where necessary, documented.

16.1. Engineering support should be available to ensure that buildings, equipment and utilities are suitably designed, installed and maintained to comply with GMP.

16.2 Engineering support may be required for
- the design of new or modified facilities and/or utilities
- the qualification of equipment
- the calibration of measuring and recording devices
- the validation of computerized systems
- the supervision of external contractors
- the maintenance of the workshops
- the training of engineering and maintenance personal in GMP.

16.3 Changes to critical facilities, equipment and services should be treated according to Section 9, Change Control.

17. Quality management

Principle

Quality Assurance is the sum total of the organised arrangements made with the object of assuring that A.I.s are of the quality required for their intended use. The assurance of product quality cannot be delegated to any single organizational unit such as Quality Control but is the responsibility of every member of the company. This should have been confirmed in a management policy statement.

17.1 Quality assurance

17.1.1 The assurance of product quality is enhanced by ensuring that all activities associated with the purchasing, storage, production, filling, control and distribution of A.I.s are carried out in a systematic and approved manner.

> NOTE 16 The presence of a Quality Assurance Department does not reduce the responsibility of other departments for product quality.

17.1.2 The introduction and maintenance of a quality assurance system can be enhanced by assigning the responsibility for such activities to a person or organizational unit.

17.1.3 The evaluation of the quality of an A.I. before being released should be based not only on the results of analytical testing but also on an evaluation of production conditions including a review of the batch production records, (Section 7.4.9). In particular, deviations from prescribed procedures or instructions should be evaluated before releasing an A.I.

17.1.4 An investigation into product complaints should be carried out, and where necessary corrective action(s) initiated.

17.1.5 Regular quality reviews of A.I.s should be written with the objective of verifying the consistency of the process. Such reviews should normally be conducted annually and include, but not necessarily be limited to:
- an evaluation of in-process control or final product test results
- an evaluation of all products which failed to meet established specifications,
- an evaluation of all processes which failed to perform as expected,
- an evaluation of any changes carried out to the process,
- an evaluation of product complaints and product recalls,
- an evaluation of on-going stability studies.

17.1.6 Auditing the quality assurance system, or parts of the system, can be an effective tool in measuring compliance with company quality objectives, (See Section 19).

17.2 Quality control

17.2.1 The responsibilities of Quality Control should be described in writing, and should include but not necessarily be limited to responsibility for:
- approving specifications;
- approving test procedures;
- approving validation plans and reports;
- sampling;
- approving reference standards;
- analytical investigations and evaluation of results;
- testing materials;
- providing analytical reports;
- approving or rejecting raw materials, packaging materials and A.I.s;
- gathering data to support retest dates, (stability testing).

17.2.2 Expertise in Quality Control can also be useful in
- evaluating the reliability of suppliers;
- validating test procedures;
- determining the identity of impurities;
- evaluating the effectiveness of cleaning;
- analysing complaint samples or returned materials.

17.2.3 To carry out its assigned responsibilities effectively Quality Control should have at its disposal:
- adequate personnel and financial resources;
- adequately trained staff;
- adequate facilities;
- well maintained and calibrated equipment;
- written and approved material specifications;
- written and approved test procedures;
- approved reference standards and reagents.

17.2.4 Documentation in Quality Control should be treated according to Chapter 7 Documentation.

17.2.5 Analysis under contract should be treated according to the principles described in Chapter 10, Contract Analysis and Manufacture.

17.3 In-Process Control (IPC)

17.3.1 In-process control points, limits, and methods should have been approved by designated persons in Quality Control.

17.3.2 The points in the process where samples for In-process controls should be taken, should be fixed in writing.

17.3.3 In-process control limits, (where necessary both warning and action limits), should be fixed in writing.

17.3.4 In-process control test procedures should be fixed in writing and critical test procedures validated.

17.3.5 Equipment used for In-process control should be maintained and calibrated as prescribed in written procedures.

17.3.6 The results of In-process control tests should be recorded in writing and be included as part of the batch records.

18. Rejection, recovery, reprocessing and returns

Principle

The treatment of materials not meeting specification should be consistent with assuring the quality of the product involved together with a responsible use of natural resources and protection of the environment. Recovery and reworking or reprocessing of rejected materials is prefered to disposal to waste.

18.1 Rejection of materials

18.1.1 Materials not meeting specification should be adequately stored to prevent unauthorized use until a decision has been taken as to their use.

18.1.2 It may not always be necessary to reject materials not meeting specification but if such non-conforming materials are used then additional controls may be necessary.

18.1.3 Use of materials not meeting specification should be approved by Quality Control.

18.1.4 When a batch of material is rejected, an evaluation as to whether other batches could have been similarly affected, should be carried out.

18.2 Recovery of materials and solvents

18.2.1 If materials are recovered for further use in an A.I. process, there should be written evidence that the subsequent use of such materials will result in a product meeting its specification.

18.2.2 Solvents should be recovered when feasable. Recovered solvents should meet an approved specification appropriate to their subsequent use.

18.2.3 The working-up of mother liquors or similar materials to obtain further materials or an A.I., if carried out, should be specifically prescribed in writing and recorded.

18.3 Reprocessing or reworking of materials

18.3.1 In general there is no objection to occasionally reprocessing materials not meeting specification by repeating all or part of the same process, however if this becomes a routine procedure, investigations should be conducted into the adequacy of the original process.

18.3.2 If it is necessary to rework materials by a process differing substantially from the original process, including the use of different solvents or reactions or purification steps, then additional tests should be carried out to verify that the resulting product not only meets the applicable specifications but also that any new and possibly unknown impurities have been adequately investigated.

18.3.3 The procedures used to reprocess or rework materials not meeting specification should be made jointly by those responsible in Production and Quality Control.

18.3.4 The procedure actually used to reprocess or rework batches of materials should be documented and included as part of the batch records.

18.3.5 Reprocessed or reworked materials should be assigned a new batch number.

18.4 Returned materials

18.4.1 Returned materials should be quarantined until a decision has been taken as to their use.

18.4.2 The decision on how to deal with returned material should be made by Quality Control taking into account the age, appearance, integrity of the original closures, storage and transport conditions, (if known) and conformance with specification of the returned material. If reprocessing or reworking is indicated this should be agreed upon between Production and Quality Control. Additional process steps or tests may then be required.

19. Stability testing and retest date

Principle

The date after which a A.I. should be retested should be based on well designed stability studies. The continuing validity of this retest date should be verified by monitoring current production. The design of stability studies should be based on internationally accepted concepts such as the ICH Harmonized Tripartite Guideline "Stability Testing of New Drug Substances and Products".

19.1 Storage conditions and retest date

19.1.1 The conditions under which A.I.s should be stored should be based on stability studies, which take into account the potential effects of storage time, storage temperature and relative humidity.

19.1.2 Based on the changes observed and measured during such studies a date should be established after which an analytical retest of the A.I. should be carried out before further use.

19.1.3 The assigned retest dates may be different for different climatic zones, depending on the differences observed or measured in the models used in the stability studies to reflect the potential climatic conditions under which the product may be stored.

19.1.4 The specification which should still be met at the end of the retest period should be available in writing. This may be different from the specification applicable at time of initial release.

19.2 Stability testing

19.2.1 The test procedures used in stability testing should have been validated.

19.2.2 The samples to be analysed in the stability testing programme should be stored in containers simulating the physical and if necessary chemical properties of those in which the product will be marketed.

19.2.3 After the initial retest date has been established this latter should be monitored by adding at least one batch a year to the stability programme.

19.2.4 When the same A.I. is produced at several sites, at least one batch a year from each site should be added to the stability programme.

19.2.5 The potential effects of critical process changes upon established retest dates should be monitored by adding samples made by the modified process to the stability programme.

19.2.6 Data collected during stability testing should be evaluated after each test point to determine if there are any unexpected trends which might indicate a significant change in the retest period. Such data should be treated according to Section 7, Documentation, Para 7.3 Test Records.

20. Complaint and recall procedures

Principle

There should be written procedures which deal with the treatment of product complaints, investigations into quality defects and product recalls.

20.1 Complaint procedures

20.1.1 All complaints, whether received orally or in writing, should be registered and investigated according to a written complaint handling procedure. Any subsequent action necessary should be taken and recorded.

20.1.2 The review of complaints should be carried out by appropriately designated personel and always include representation from Quality Control.

20.1.3 Records of complaints should be so retained that trends, product- related frequencies, and severities can be evaluated with a view to taking additional, and if necessary, immediate corrective action.

20.2 Recall procedures

20.2.1 There should be a written procedure available which lays down under what circumstances a recall of a A.I. should be considered.

20.2.2 The recall procedure should designate who should be involved in evaluating the information which may result in a recall, how a recall should be initiated, who should be informed about the recall, and how the recalled material should be treated.

20.2.3 In the event of a serious and potentially life-threatening situation local and national authorities should be informed and their advice sought.

21. Self-inspections

Principle

Self Inspections should be conducted in order to monitor the implementation and the compliance with Good Manufacturing Practices and to propose necessary corrective measures.

20.1 In order to verify the compliance with the GMP principles for A.I.s described in these guidelines, manufacturers should designate an expert or team of experts to conduct regular Self-Inspections.

20.2 Self-inspection findings and the corrective action(s), where necessary, should be recorded.

20.3 Management is responsible for implementing the corrective actions derived from the findings.

Appendix I: retention periods

Principle

The purpose of generating records of manufacturing activities is to be able to investigate, at a later date, the exact circumstances surrounding the manufacture of an A.I. It is thus necessary to retain such records and the associated samples for a sufficient period of time during which such investigations may need to be carried out. As, at the end of the retest period for an A.I., there may be a considerable amount of the batch incorporated into medicinal or veterinary products which are still on the market, the selected retention period must take account of this fact.

1. Documentation

1.1 There should be written procedures which lay down how long documents should be retained. In general this should be at least 6 years unless otherwise justified

1.2 Documents which should fall under the above ruling include, but are not limited to are:

- material receipt records,
- material testing and release records,
- batch production records for A.I.s,
- batch analytical records for A.I.s,
- batch release records for A.I.s,
- batch production records for critical intermediates,
- batch analytical records for critical intermediates,
- equipment cleaning records for that equipment used to manufacture A.I.s
- maintenance and calibration records for equipment used in the manufacture of
- change control records,
- environmental monitoring records, including temperature recording for critical areas,as well as microbiological monitoring records,
- packaging records,
- distribution records,
- customer complaint investigation records,
- all records associated with any product recalls.

1.3 Other documents which should be retained are, for example

- product development reports,
- specifications and test procedures for materials,
- validation reports of the analytical test procedures,
- equipment layout plans,
- equipment installations reports, (IQ Reports)
- equipment acceptance reports, (OQ Reports)
- the records supporting the validity of the process, (Validation Reports)

The retention period of these documents should be no shorter than the period given in Para 1.1 above and may need to be much longer if, for example, the equipment life is much longer than the period given in Para 1.1.

2. Samples

2.1 The retention period for samples of raw materials should by one year after release. Samples of hazardous, gaseous, inflammable, environmentally dangerous, or unstable raw materials or intermediates need not be retained. Only representative samples of naturally occuring raw materials need to be retained for the time specified above.

2.2 Samples of A.I.s should be retained for a minimum of 12 months after the assigned retest date of the batch. If this retest date is extended then the retention period for the sample should be correspondingly extended.

2.3 The purpose of retaining a sample is to carry out, at a later date, an analytical investigation into the quality of the sample. Samples should therefore be

- stored in a container, and under conditions which are selected to prevent deterioration,
- stored in sufficient quantities to carry out at least two full analyses of the material.

2.4 Retention samples are not intended to be used to confirm retest periods. If such confirmation is required, the samples should be stored in containers and under conditions which simulate the conditions applicable to the marketed product, (See Chapter 17 Stabilitty Testing and Retest Dates).

Appendix II: references

1. Guide to Good Manufacturing Practice for Medicinal Products, in "The Rules governing Medicinal Products in the European Community", Volume IV, January 1992.

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3. "Bonnes Pratiques de Fabrication des produits chimiques à usage pharmaceutique", sponsored by SICOS Biochimie, Paris, (May 1989).

4. Good Manufacturing Practices, "Guidelines" for the production and control of Bulk Pharmaceutical Chemicals, 4th Edition, sponsored by Aschimfarma, Milan, Italy, (March 1991)

5. "Bulk Pharmaceutical Chemicals", Pharmaceutical Quality Group Monograph, The Institute of Quality Assurance, London, 1992, ISBN 0 906810 22 1.

6. "Recommendations for Good Manufacturing Practices for Active Ingredients", VFA Monograph, approved by VFA, Bonn, Germany, March 1995.

7. "Good Manufacturing Practices, Guidance for Bulk Pharmaceutical Chemicals Manufacturers", edited by the BPC Committee, CEFIC, Bruxelles, ("The CEFIC Draft"), (May 1995).

8. "Concepts for the Process Validation of Bulk Pharmaceutical Chemicals" edited by the Pharmaceutical Manufacturers Association, QC Section, Bulk Pharmaceuticals Committee, in Pharmaceutical Technology Europe, January 1994.

9. Commission Directive of 13 June 1991 laying down the principles and guidelines of good manufacturing practices for medicinal products for human use, (91/356/EEC) - Official Journal of the European Communities; N° L 193 of 17 July 1991.

10. Commission Directive of 23 July 1991 laying down the principles and guidelines of good manufacturing practices for veterinary medicinal products (91/412/EEC) - Official Journal of the European Communities; N° L 228 of 17 Aug. 1991.

11. Good Manufacturing Practices for active pharmaceutical ingredients (bulk drug substances) in WHO Expert Committee on "Specifications for Pharmaceutical Preparations, 32nd Report", Geneva, 1992, ISB 92 4 1208236.

12. Current Good Manufacturing Practices for Finished Pharmaceuticals, US Food and Drug Administration, 21 CFR Part 211.

13. "Guide to Inspection of Bulk Pharmaceutical Chemicals", US Food and Drug Administration, Revised Edition, May 1994.

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FDA Regulation of Bulk Pharmaceutical Chemical Production, D.B. Barr et al, in Pharmaceutical Technology; September 1993.

FDA Regulation of Bulk Pharmaceutical Chemicals - An Industrial Commentary, N. C. Franklin et al in Pharmaceutical Technology, Part I, October 1994, Part II November 1994.

An FDA Perspective on Bulk Pharmaceutical Chemical GMPs, E. Rivera Martinez, in Pharmaceutical Technology, May / June 1994.

ICH - Harmonized Tripartite Guideline on Stability Testing of New Drug Substances and Products, October 1993.

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