



EUROPEAN COMMISSION  
HEALTH AND CONSUMERS DIRECTORATE-GENERAL  
Public Health and Risk Assessment  
**Medicinal products – quality, safety and efficacy**

Brussels, <date>

## **EudraLex**

### **The Rules Governing Medicinal Products in the European Union**

#### **Volume 4**

#### **EU Guidelines for**

#### **Good Manufacturing Practice for**

#### **Medicinal Products for Human and Veterinary Use**

#### **Part 1**

#### **Chapter 3: Premises and Equipment**

**Legal basis for publishing the detailed guidelines:** Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and Article 51 of Directive 2001/82/EC on the Community code relating to veterinary medicinal products. This document provides guidance for the interpretation of the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Directive 2003/94/EC for medicinal products for human use and Directive 91/412/EEC for veterinary use.

**Status of the document:** Revision.

**Reasons for changes:** The only change is to section 6 as part of the improved guidance on prevention of cross-contamination involving also Chapter 5 and includes reference to a new complementary toxicological assessment guidance.

**Deadline for coming into operation:** <6 months from publication>

## **Principle**

Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of products.

## **Premises**

### ***General***

3.1 Premises should be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products.

3.2 Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They should be cleaned and, where applicable, disinfected according to detailed written procedures.

3.3 Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the medicinal products during their manufacture and storage, or the accurate functioning of equipment.

3.4 Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals.

3.5 Steps should be taken in order to prevent the entry of unauthorised people. Production, storage and quality control areas should not be used as a right of way by personnel who do not work in them.

### ***Production Area***

3.6 Cross- contamination should be avoided for all products by appropriate design and operation of manufacturing facilities. The measures to prevent cross-contamination should be commensurate with the risks. Quality Risk Management principles should be used to assess and control the risks. Risk assessment should include among other parameters a toxicological evaluation of the products being manufactured (see Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities).

Dedicated facilities are required for manufacturing when a medicinal product presents a risk:

- a) Which cannot be adequately controlled by operational and/ or technical measures or
- b) Scientific data does not support threshold values (e.g. allergenic potential from highly sensitising materials such as beta lactams) or
- c) Threshold values derived from the toxicological evaluation are below the levels of detection

Further guidance including some exemptions could be found in Chapter 5 and in Annex 2, 3, 4, 5 of the EU detailed guidelines on GMP and the guideline on setting health based exposure

limits for use in risk identification in the manufacture of different medicinal products in shared facilities.<sup>1</sup>

3.7 Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

3.8 The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimise the risk of confusion between different medicinal products or their components, to avoid cross-contamination and to minimise the risk of omission or wrong application of any of the manufacturing or control steps.

3.9 Where starting and primary packaging materials, intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be smooth, free from cracks and open joints, and should not shed particulate matter and should permit easy and effective cleaning and, if necessary, disinfection.

3.10 Pipework, light fittings, ventilation points and other services should be designed and sited to avoid the creation of recesses which are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.

3.11 Drains should be of adequate size, and have trapped gullies. Open channels should be avoided where possible, but if necessary, they should be shallow to facilitate cleaning and disinfection.

3.12 Production areas should be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity and filtration) appropriate both to the products handled, to the operations undertaken within them and to the external environment.

3.13 Weighing of starting materials usually should be carried out in a separate weighing room designed for such use.

3.14 In cases where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of dry products), specific provisions should be taken to avoid cross contamination and facilitate cleaning.

3.15 Premises for the packaging of medicinal products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.

3.16 Production areas should be well lit, particularly where visual on-line controls are carried out.

3.17 In-process controls may be carried out within the production area provided they do not carry any risk to production.

### ***Storage Areas***

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3.18 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediate, bulk and finished products, products in quarantine, released, rejected, returned or recalled.

3.19 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.

3.20 Receiving and dispatch bays should protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned where necessary before storage.

3.21 Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorised personnel. Any system replacing the physical quarantine should give equivalent security.

3.22 There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.

3.23 Segregated areas should be provided for the storage of rejected, recalled or returned materials or products.

3.24 Highly active materials or products should be stored in safe and secure areas.

3.25 Printed packaging materials are considered critical to the conformity of the medicinal product and special attention should be paid to the safe and secure storage of these materials.

#### ***Quality Control Areas***

3.26 Normally, Quality Control laboratories should be separated from production areas. This is particularly important for laboratories for the control of biologicals, microbiologicals and radioisotopes, which should also be separated from each other.

3.27 Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples and records.

3.28 Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc.

3.29 Special requirements are needed in laboratories handling particular substances, such as biological or radioactive samples.

#### ***Ancillary Areas***

3.30 Rest and refreshment rooms should be separate from other areas.

3.31 Facilities for changing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not directly communicate with production or storage areas.

3.32 Maintenance workshops should as far as possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

3.33 Animal houses should be well isolated from other areas, with separate entrance (animal access) and air handling facilities.

### **Equipment**

3.34 Manufacturing equipment should be designed, located and maintained to suit its intended purpose.

3.35 Repair and maintenance operations should not present any hazard to the quality of the products.

3.36 Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned according to detailed and written procedures and stored only in a clean and dry condition.

3.37 Washing and cleaning equipment should be chosen and used in order not to be a source of contamination.

3.38 Equipment should be installed in such a way as to prevent any risk of error or of contamination.

3.39 Production equipment should not present any hazard to products. Parts of production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.

3.40 Balances and measuring equipment of an appropriate range and precision should be available for production and control operations.

3.41 Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.

3.42 Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.

3.43 Distilled, deionised and, where appropriate, other water pipes should be sanitised according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

3.44 Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labelled as defective.



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#### **Chapter 5: Production**

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**Status of the document:** Revision.

**Reasons for changes:** Changes have been made to sections 17 to 20 to improve the guidance on prevention of cross-contamination and to refer to toxicological assessment guidance. Changes were also introduced in sections 26 to 28 on the qualification of suppliers in order to reflect the legal obligation of manufacturing authorisation holders to ensure that active substances are produced in accordance with GMP. The changes include supply chain traceability. Section (33) is inserted to clarify and harmonise expectations of manufacturers regarding the testing of starting materials while section (68) introduces guidance on notification of restrictions in supply.

**Deadline for coming into operation:** 6 months from publication

## **Principle**

Production operations must follow clearly defined procedures; they must comply with the principles of Good Manufacturing Practice in order to obtain products of the requisite quality and be in accordance with the relevant manufacturing and marketing authorisations.

## **General**

- 5.1 Production should be performed and supervised by competent people.
- 5.2 All handling of materials and products, such as receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.
- 5.3 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled with the prescribed data.
- 5.4 Damage to containers and any other problem which might adversely affect the quality of a material should be investigated, recorded and reported to the Quality Control Department.
- 5.5 Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.
- 5.6 Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.
- 5.7 All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation.
- 5.8 Checks on yields, and reconciliation of quantities, should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.
- 5.9 Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination.
- 5.10 At every stage of processing, products and materials should be protected from microbial and other contamination.
- 5.11 When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly active or sensitising materials.
- 5.12 At all times during processing, all materials, bulk containers, major items of equipment and where appropriate rooms used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and batch number. Where applicable, this indication should also mention the stage of production.

- 5.13 Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colours to indicate status (for example, quarantined, accepted, rejected, clean ...).
- 5.14 Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.
- 5.15 Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be approved in writing by a competent person, with the involvement of the Quality Control Department when appropriate.
- 5.16 Access to production premises should be restricted to authorised personnel.

### **Prevention of cross-contamination in production**

- 5.17 Normally, the production of non-medicinal products should be avoided in areas and with equipment destined for the production of medicinal products but in exceptional circumstances could be allowed where the measures to prevent cross contamination with medicinal products described below and in Chapter 3 can be applied. The production of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of medicinal products.

- 5.18 Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapours, sprays, genetic material or organisms from active substances, other starting materials, products in process, from residues on equipment, and from operators' clothing. The significance of this risk varies with the type of contaminant and of product being contaminated. Products in which cross contamination is likely to be most significant are those administered by injection and those given over a long time.

Cross contamination should be avoided by robust design of the premises, equipment and processes which take place within a manufacturing facility. This should be supported by appropriate procedures and technical or organizational measures, including reproducible cleaning and decontamination processes of validated effectiveness.

- 5.19 A toxicological evaluation should be the basis for the establishment of threshold values in relation to the products manufactured (see Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities). Where the toxicological evaluation supports a threshold value, this should be used as an input parameter in risk assessment. A Quality Risk Management approach should be used based upon this toxicological evaluation and the potential cross contamination risks presented by the products manufactured. Factors including; facility/equipment design, personnel flow, physico-chemical characteristics of the active substance, process characteristics, cleaning processes and analytical capabilities relative to the threshold values for products should also be taken into account. The outcome of the Quality Risk Management process should be the basis for determining the necessity for and extent to which equipment and facilities should be dedicated to a particular

product or product family. This may range from dedicating specific product contact parts to dedication of the entire manufacturing facility. It may be acceptable to confine manufacturing activities to a segregated, self contained production area within a multiproduct facility, where justified.

- 5.20 Technical and organisational measures to mitigate risks of cross-contamination could include, but are not limited to, the following:

#### Technical Measures

- dedicated facilities,
- self-contained production areas having separate processing equipment and separate HVAC systems. It may also be desirable to isolate certain utilities from those used in other areas.
- design of manufacturing process, facility and equipment to minimize opportunities for cross contamination during processing, maintenance and cleaning
- use of “closed systems” for processing and material / product transfer between equipment,
- use of physical barrier systems, including isolators, as containment measures
- Controlled removal of dust close to source of the contaminant e.g. through localised extraction
- dedication of processing equipment, dedication of product contact parts or dedication of selected parts which are harder to clean (e.g. filters), dedication of maintenance tools
- use of disposable technologies
- use of equipment designed for ease of cleaning
- appropriate use of air-locks and pressure cascade to confine potential airborne contaminant within a specified area
- minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air
- use of automatic clean in place systems of validated effectiveness,
- for common general wash areas, separation of equipment washing, drying and storage areas,

#### Organisational Measures

- Dedicating the whole manufacturing facility or a self contained production area on a campaign basis (dedicated by separation in time) followed by a cleaning process of validated effectiveness,
- Keeping protective clothing inside areas where products with high risk of cross contamination are processed,

- Cleaning verification after each product campaign instead of a cleaning validation should be considered as a detectability tool to support effectiveness of the Quality Risk Management approach,
- Cleaning of working areas and surfaces followed by execution of a comprehensive sampling protocol for critical surfaces
- Use of air samples and wipe/swab samples taken in adjoining areas outside the working area to demonstrate the efficiency of mitigation measures for airborne and mechanical transfer of contaminant,
- Specific measures for waste handling, contaminated rinsing water and soiled gowning,
- Recording of spills, accidental events or deviations from procedures
- Design of cleaning processes for manufacturing equipment and building facilities such that the cleaning processes in themselves do not present a cross contamination risk.
- Design of detailed records for cleaning processes to assure completion of cleaning in accordance with approved procedures and use of cleaning status labels on equipment and manufacturing areas,
- Use of common general wash areas on a campaign basis.
- Monitoring of working behaviour to ensure training effectiveness and compliance with the relevant procedural controls.

5.21 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to set procedures.

### **Validation**

5.22 Validation studies should reinforce Good Manufacturing Practice and be conducted in accordance with defined procedures. Results and conclusions should be recorded.

5.23 When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.

5.24 Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process, should be validated.

5.25 Processes and procedures should undergo periodic critical re-validation to ensure that they remain capable of achieving the intended results.

### **Starting materials**

5.26 The selection, qualification, approval and maintenance of suppliers of starting materials, together with their purchase and acceptance, should be documented as part of the pharmaceutical quality system. The level of supervision should be proportionate to the risks posed by the individual materials, taking account of their source, manufacturing

process, supply chain complexity and the final use to which the material is put in the medicinal product. The supporting evidence for each supplier / material approval should be maintained. Staff involved in these activities should have a current knowledge of the suppliers, the supply chain and the associated risks involved. Where possible starting materials should be purchased directly from the manufacturer of the starting material..

The quality requirements established by the manufacturer for the starting materials should be discussed and agreed with the suppliers. Appropriate aspects of the production, and control, including handling, labelling, packaging and distribution requirements, complaints, recalls and rejection procedures should be documented in a quality agreement or specification.

- 5.27 For the approval and maintenance of suppliers of active substances and excipients, the following is required:

#### Active substances

Supply chain traceability should be established and the associated risks, from active substance starting materials to the finished medicinal product, should be formally assessed and periodically verified. Appropriate measures should be put in place to reduce risks to the quality of the active substance.

The supply chain and traceability records for each active substance (including active substance starting materials) should be available and be retained by the EEA based manufacturer or importer of the medicinal product.

Audits should be carried out at the manufacturers and distributors of active substances to confirm that they comply with the relevant good manufacturing practice and good distribution practice requirements. The holder of the manufacturing authorization shall verify such compliance either by himself or through an entity acting on his behalf under a contract. For veterinary medicinal products, audits should be conducted based on risk.

Audits should be of an appropriate duration and scope to ensure that a full and clear assessment of GMP is made; consideration should be given to potential cross-contamination from other materials on site. The report should fully reflect what was done and seen on the audit with any deficiencies clearly identified. Corrective and preventive actions should be implemented.

Further audits should be undertaken at intervals defined by the quality risk management process to ensure the maintenance of standards and continued use of the approved supply chain.

#### Excipients

Excipients which are considered to pose a particular risk to the quality of the medicinal product, based on formalised quality risk management, should be given similar attention to those for active substances.

- 5.28 For each delivery of starting material the containers should be checked for integrity of package, including tamper evident seal where relevant, and for correspondence between the delivery note, the supplier's labels and approved supplier information maintained by the medicinal product manufacturer. The receiving checks on each delivery should be documented.

- 5.29 If one material delivery is made up of different batches, each batch must be considered as separate for sampling, testing and release.
- 5.30 Starting materials in the storage area should be appropriately labelled (see Chapter 5, item 13). Labels should bear at least the following information:
- The designated name of the product and the internal code reference where applicable; a batch number given at receipt;
  - Where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected);
  - Where appropriate, an expiry date or a date beyond which retesting is necessary.

When fully computerised storage systems are used, all the above information need not necessarily be in a legible form on the label.

- 5.31 There should be appropriate procedures or measures to assure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified (see Chapter 6, item 13).
- 5.32 Only starting materials which have been released by the Quality Control Department and which are within their shelf life should be used.
- 5.33 Manufacturers of finished products are responsible for any testing of starting materials as described in the marketing authorisation dossier. They can utilise partial or full test results from the approved starting material manufacturer but must, as a minimum, perform identification testing of each batch themselves according to annex 8.

The rationale for the outsourcing of this testing should be justified and documented and the following requirements should be fulfilled:

- a) A formal agreement should be signed, according to chapter 7, between the finished product manufacturer and the starting material manufacturer. Among the respective responsibilities described in the formal agreement, special attention should be paid to those related to the distribution conditions (transport, wholesaling, storage and delivery) in order to maintain the quality characteristics of the starting materials and to ensure that test results remain applicable to the delivered material.
- b) The finished product manufacturer should perform audits at appropriate intervals at the site(s) carrying out the testing (including sampling) of the starting materials in order to assure compliance with Good Manufacturing Practice and with the specifications and testing methods described in the Marketing Authorisation dossier.
- c) The certificate of analysis provided by the starting material manufacturer should be signed by a designated person with appropriate qualifications and experience. This person should ensure that each batch has been manufactured and checked for compliance with the requirements of the formal agreement.
- d) The finished product manufacturer should have a significant experience in dealing with the starting material manufacturer including assessment of batches previously received and the history of compliance before reducing in-house testing. Any significant change in the manufacturing or testing processes should be considered.

e) The finished product manufacturer should also perform a full analysis at appropriate intervals and compare the results with the supplier's certificate of analysis in order to check the reliability of the latter. Should this testing identify any discrepancy then an investigation should be performed and appropriate measures taken. The acceptance of certificate of analysis from the supplier should be discontinued until these measures are completed.

Notes:

1. A similar approach should apply to packaging materials as stated in GMP part I, 5.41.
2. Identity testing of starting materials should be performed according to the methods and the specifications of the relevant Marketing Authorisation dossier.

- 5.34 Starting materials should only be dispensed by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.
- 5.35 Each dispensed material and its weight or volume should be independently checked and the check recorded.
- 5.36 Materials dispensed for each batch should be kept together and conspicuously labelled as such.

#### **Processing operations: intermediate and bulk products**

- 5.37 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues or documents not required for the current operation.
- 5.38 Intermediate and bulk products should be kept under appropriate conditions.
- 5.39 Critical processes should be validated (see "Validation" in this Chapter).
- 5.40 Any necessary in-process controls and environmental controls should be carried out and recorded.
- 5.41 Any significant deviation from the expected yield should be recorded and investigated.

#### **Packaging materials**

- 5.42 The purchase, handling and control of primary and printed packaging materials shall be accorded attention similar to that given to starting materials.
- 5.43 Particular attention should be paid to printed materials. They should be stored in adequately secure conditions such as to exclude unauthorised access. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by authorised personnel following an approved and documented procedure.
- 5.44 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.

5.45 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and this disposal recorded.

### **Packaging operations**

5.46 When setting up a programme for the packaging operations, particular attention should be given to minimising the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation.

5.47 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents previously used, if these are not required for the current operation. The line-clearance should be performed according to an appropriate check-list.

5.48 The name and batch number of the product being handled should be displayed at each packaging station or line.

5.49 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the Packaging Instructions.

5.50 Containers for filling should be clean before filling. Attention should be given to avoid and remove any contaminants such as glass fragments and metal particles.

5.51 Normally, filling and sealing should be followed as quickly as possible by labelling. If it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabelling can occur.

5.52 The correct performance of any printing operation (for example code numbers, expiry dates) to be done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand which should be re-checked at regular intervals.

5.53 Special care should be taken when using cut-labels and when over-printing is carried out off-line. Roll-feed labels are normally preferable to cut-labels, in helping to avoid mix-ups.

5.54 Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.

5.55 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

5.56 On-line control of the product during packaging should include at least checking the following:

a) General appearance of the packages;

b) Whether the packages are complete;

- c) Whether the correct products and packaging materials are used;
- d) Whether any over-printing is correct;
- e) Correct functioning of line monitors.

Samples taken away from the packaging line should not be returned.

- 5.57 Products which have been involved in an unusual event should only be reintroduced into the process after special inspection, investigation and approval by authorised personnel. Detailed record should be kept of this operation.
- 5.58 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.
- 5.59 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure should be followed if uncoded printed materials are returned to stock.

### **Finished products**

- 5.60 Finished products should be held in quarantine until their final release under conditions established by the manufacturer.
- 5.61 The evaluation of finished products and documentation which is necessary before release of product for sale are described in Chapter 6 (Quality Control).
- 5.62 After release, finished products should be stored as usable stock under conditions established by the manufacturer.

### **Rejected, recovered and returned materials**

- 5.63 Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed. Whatever action is taken should be approved and recorded by authorised personnel.
- 5.64 The reprocessing of rejected products should be exceptional. It is only permitted if the quality of the final product is not affected, if the specifications are met and if it is done in accordance with a defined and authorised procedure after evaluation of the risks involved. Record should be kept of the reprocessing.
- 5.65 The recovery of all or part of earlier batches which conform to the required quality by incorporation into a batch of the same product at a defined stage of manufacture should be authorised beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf life. The recovery should be recorded.

- 5.66 The need for additional testing of any finished product which has been reprocessed, or into which a recovered product has been incorporated, should be considered by the Quality Control Department.
- 5.67 Products returned from the market and which have left the control of the manufacturer should be destroyed unless without doubt their quality is satisfactory; they may be considered for re-sale, re-labelling or recovery in a subsequent batch only after they have been critically assessed by the Quality Control Department in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for re-issue or re-use, although basic chemical reprocessing to recover active ingredient may be possible. Any action taken should be appropriately recorded.

### **Product shortage due to manufacturing constraints**

- 5.68 "The holder of a marketing authorisation for a medicinal product should, within the limits of their responsibilities, ensure appropriate and continued supplies of that medicinal product to pharmacies and persons authorised to supply medicinal products<sup>2</sup>. The marketing authorisation holder should be informed in a timely manner in case of any constraints in manufacturing operations which may result in an abnormal restriction in the supply of a medicinal product. The holder should also notify the competent authority if the product ceases to be placed on the market of the Member State, either temporarily or permanently. Such notification shall, otherwise than in exceptional circumstances, be made no less than 2 months before the interruption in the placing on the market of the product<sup>3</sup>

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<sup>2</sup> Article 81 of Directive 2001/83/EC, as amended

<sup>3</sup> Article 23a of Directive 2001/83/EC



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**Status of the document:** Revision

**Reasons for changes:**

Inclusion of a new section on Technical transfer of testing methods and other items such as out of specification results.

**Deadline for coming into operation:** <6 months from publication>

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### **Principle**

This chapter should be read in conjunction with all relevant sections of the GMP guide  
Quality Control is concerned with sampling, specifications and testing as well as the organisation, documentation and release procedures which ensure that the necessary and

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relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory. Quality Control is not confined to laboratory operations, but must be involved in all decisions which may concern the quality of the product. The independence of Quality Control from Production is considered fundamental to the satisfactory operation of Quality Control.

### **General**

- 6.1 Each holder of a manufacturing authorisation should have a Quality Control Department. This department should be independent from other departments, and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his disposal. Adequate resources must be available to ensure that all the Quality Control arrangements are effectively and reliably carried out.
- 6.2 The principal duties of the head of Quality Control are summarised in Chapter 2. The Quality Control Department as a whole will also have other duties, such as to establish, validate and implement all quality control procedures, oversee the control of the reference and/or retention samples of materials and products when applicable, ensure the correct labelling of containers of materials and products, ensure the monitoring of the stability of the products, participate in the investigation of complaints related to the quality of the product, etc. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.
- 6.3 Finished product assessment should embrace all relevant factors, including production conditions, results of in-process testing, a review of manufacturing (including packaging) documentation, compliance with Finished Product Specification and examination of the final finished pack.
- 6.4 Quality Control personnel should have access to production areas for sampling and investigation as appropriate.

### **Good Quality Control Laboratory Practice**

- 6.5 Control laboratory premises and equipment should meet the general and specific requirements for Quality Control areas given in Chapter 3. In particular, the microbiological laboratory should be arranged so as to minimize risk of cross-contamination. Laboratory equipment should not be routinely moved between high risk areas to avoid accidental cross-contamination.
- 6.6 The personnel, premises, and equipment in the laboratories should be appropriate to the tasks imposed by the nature and the scale of the manufacturing operations. The use of outside laboratories, in conformity with the principles detailed in Chapter 7, Contract Analysis, can be accepted for particular reasons, but this should be stated in the Quality Control records.

#### ***Documentation***

- 6.7 Laboratory documentation should follow the principles given in Chapter 4. An important part of this documentation deals with Quality Control and the following details should be readily available to the Quality Control Department:
  - specifications;
  - procedures describing sampling, testing, records (including test worksheets and/or laboratory notebooks), recording and verifying;

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- a procedure for the investigation of Out Of Specification and anomalous results and Out Of Trend results;
  - procedures for and records of the calibration/qualification of instruments and maintenance of equipment;
  - testing reports and/or certificates of analysis;
  - data from environmental (air, water and others utilities) monitoring, where required;
  - validation records of test methods, where applicable
- 6.8 Any Quality Control documentation relating to a batch record should be retained following the principles given in chapter 4 on retention of batch documentation.
- 6.9 Some kinds of data (e.g. tests results, yields, environmental controls) should be recorded in a manner permitting trend evaluation. Any out of trend or out of specification data should be addressed and subject to investigation.
- 6.10 In addition to the information which is part of the batch documentation, other raw data such as laboratory notebooks and/or records should be retained and readily available

### *Sampling*

- 6.11 The sample taking should be done and recorded in accordance with approved written procedures that describe:
- the method of sampling;
  - the equipment to be used;
  - the amount of the sample to be taken;
  - instructions for any required sub-division of the sample;
  - the type and condition of the sample container to be used;
  - the identification of containers sampled;
  - any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials;
  - the storage conditions;
  - instructions for the cleaning and storage of sampling equipment.
- 6.12 Samples should be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process). The sampling plan used should be appropriately justified.
- 6.13 Sample containers should bear a label indicating the contents, with the batch number, the date of sampling and the containers from which samples have been drawn. They should be managed in a manner to minimize the risk of mix-up and to protect the samples from adverse storage conditions.
- 6.14 Further guidance on reference and retention samples is given in Annex 19.

### *Testing*

- 6.15 Testing methods should be validated. A laboratory that is using a testing method and which did not perform the original validation (e.g. the use of a compendial method), should verify the appropriateness of the testing method. All testing operations described in the marketing authorisation or technical dossier should be carried out

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- according to the approved methods.
- 6.16 The results obtained should be recorded, trended and checked to make sure that they are consistent with each other. Any calculations should be critically examined.
- 6.17 The tests performed should be recorded and the records should include at least the following data:
- a) name of the material or product and, where applicable, dosage form;
  - b) batch number and, where appropriate, the manufacturer and/or supplier;
  - c) references to the relevant specifications and testing procedures;
  - d) test results, including observations and calculations, and reference to any certificates of analysis;
  - e) dates of testing;
  - f) initials of the persons who performed the testing;
  - g) initials of the persons who verified the testing and the calculations, where appropriate;
  - h) a clear statement of approval or rejection (or other status decision) and the dated signature of the designated responsible person.
- 6.18 All the in-process controls, including those made in the production area by production personnel, should be performed according to methods approved by Quality Control and the results recorded.
- 6.19 Special attention should be given to the quality of laboratory reagents, solutions, glassware, reference standards and culture media. They should be prepared and controlled in accordance with written procedures.
- 6.20 Reference standards should be certified, qualified and verified as suitable for its intended use.
- 6.21 Culture media should be prepared in accordance with the manufacturer's requirements unless scientifically justified. The performance of all culture media should be verified prior to use.
- 6.22 Laboratory reagents, solutions, reference standards and culture media should be marked with the preparation and opening date and the signature of the person who prepared them. Their in-use shelf life should be established / documented and scientifically justified. The expiry date of unstable reagents and culture media should be indicated on the label, together with specific storage conditions. In addition, for volumetric solutions, the last date of standardisation and the last current factor should be indicated.
- 6.23 Where necessary, the date of receipt of any substance used for testing operations (e.g. reagents, solutions and reference standards) should be indicated on the container. Instructions for use and storage should be followed. In certain cases it may be necessary to carry out an identification test and/or other testing of reagent materials upon receipt or before use.
- 6.24 Animals used for testing components, materials or products, should, where appropriate, be quarantined before use. They should be maintained and controlled in a manner that assures their suitability for the intended use. They should be identified, and adequate records should be maintained, showing the history of their use.
- 6.25 Microbiological media and strains should be decontaminated and disposed of in a manner to prevent the cross-contamination and retention of residues. The in-use shelf

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life of microbiological media should be established, ~~and~~ documented and scientifically justified.

***On-going stability programme***

- 6.26 After marketing, the stability of the medicinal product should be monitored according to a continuous appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of impurities or dissolution profile) associated with the formulation in the marketed package.
- 6.27 The purpose of the on-going stability programme is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the labelled storage conditions.
- 6.28 This mainly applies to the medicinal product in the package in which it is sold, but consideration should also be given to the inclusion in the programme of bulk product. For example, when the bulk product is stored for a long period before being packaged and/or shipped from a manufacturing site to a packaging site, the impact on the stability of the packaged product should be evaluated and studied under ambient conditions. In addition, consideration should be given to intermediates that are stored and used over prolonged periods. Stability studies on reconstituted product are performed during product development and need not be monitored on an on-going basis. However, when relevant, the stability of reconstituted product can also be monitored.
- 6.29 The on-going stability programme should be described in a written protocol following the general rules of Chapter 4 and results formalised as a report. The equipment used for the on-going stability programme (stability chambers among others) should be qualified and maintained following the general rules of Chapter 3 and annex 15.
- 6.30 The protocol for an on-going stability programme should extend to the end of the shelf life period and should include, but not be limited to, the following parameters:
- number of batch(es) per strength and different batch sizes, if applicable
  - relevant physical, chemical, microbiological and biological test methods
  - acceptance criteria
  - reference to test methods
  - description of the container closure system(s)
  - testing intervals (time points)
  - description of the conditions of storage (standardised ICH/VICH conditions for long term testing, consistent with the product labelling, should be used)
  - other applicable parameters specific to the medicinal product.
- 6.31 The protocol for the on-going stability programme can be different from that of the initial long-term stability study as submitted in the marketing authorisation dossier provided that this is justified and documented in the protocol (for example the frequency of testing, or when updating to ICH/VICH recommendations).
- 6.32 The number of batches and frequency of testing should provide a sufficient amount of data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability programme (unless none are produced during that year). For products where on-going stability monitoring would normally require testing using animals and no appropriate alternative, validated techniques are available, the

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frequency of testing may take account of a risk-benefit approach. The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol.

- 6.33 In certain situations, additional batches should be included in the on-going stability programme. For example, an on-going stability study should be conducted after any significant change or significant deviation to the process or package. Any reworking, reprocessing or recovery operation should also be considered for inclusion.
- 6.34 Results of on-going stability studies should be made available to key personnel and, in particular, to the Qualified Person(s). Where on-going stability studies are carried out at a site other than the site of manufacture of the bulk or finished product, there should be a written agreement between the parties concerned. Results of on-going stability studies should be available at the site of manufacture for review by the competent authority.
- 6.35 Out of specification or significant atypical trends should be investigated. Any confirmed out of specification result, or significant negative trend, should be reported to the relevant competent authorities. The possible impact on batches on the market should be considered in accordance with Chapter 8 of the GMP Guide and in consultation with the relevant competent authorities.
- 6.36 A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.

#### **Technical transfer of testing methods**

- 6.37 Prior to transferring a test method, the transferring site should verify that the test method(s) comply with those as described in the Marketing Authorisation or the relevant technical dossier. The original validation of the test method(s) should be reviewed to ensure compliance with current ICH/VICH requirements. A gap analysis should be performed and documented to identify any supplementary validation that should be performed, prior to commencing the technical transfer process.
- 6.38 The transfer of test methodology from one laboratory (transferring laboratory) to another laboratory (receiving laboratory) should be described in a written protocol.
- 6.39 The protocol should include, but not be limited to, the following parameters:
- identification of the relevant test method(s) undergoing transfer
  - Identification of the additional training requirements
  - identification of standards and samples to be tested by both laboratories
  - identification of any special transport and storage conditions of test items
  - identification of the testing to be performed
  - the acceptance criteria which should be based upon the current validation study of the methodology and with respect to ICH/VICH requirements
- 6.40 Deviations from the protocol should be investigated prior to closure of the technical transfer process. The technical transfer report should document the comparative outcome of the process and should identify areas requiring further test method revalidation, if applicable.
- 6.41 Where appropriate, specific requirements described in others European Guidelines, should be addressed for the transfer of particular testing methods (e.g Near Infrared Spectroscopy).



EUROPEAN COMMISSION  
HEALTH AND CONSUMERS DIRECTORATE-GENERAL  
Public Health and Risk Assessment  
**Medicinal products – quality, safety and efficacy**

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Brussels, <date>

## **EudraLex**

### **The Rules Governing Medicinal Products in the European Union**

#### **Volume 4**

#### **EU Guidelines for**

#### **Good Manufacturing Practice for**

#### **Medicinal Products for Human and Veterinary Use**

#### **Part 1**

#### **Chapter 8: Complaints, Quality Defects and Product Recalls**

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**Legal basis for publishing the detailed guidelines:** Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and Article 51 of Directive 2001/82/EC on the Community code relating to veterinary medicinal products. This document provides guidance for the interpretation of the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Directive 2003/94/EC for medicinal products for human use and Directive 91/412/EEC for veterinary use.

**Status of the document:** Revision

**Reasons for changes:**

- To reflect Quality Risk Management principles to be applied when investigating quality defects/complaints and when making decisions in relation to product recalls or other risk-mitigating actions.
- To emphasise the need for the cause(s) of quality defects/complaints to be investigated and determined, and that appropriate preventative actions are put in place to guard against a recurrence of the issue.
- To clarify expectations and responsibilities in relation to the reporting of quality defects to the Supervisory Authority.

**Deadline for coming into operation:** <6 months from publication>

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### **Principle**

In order to protect public and animal health, a system and appropriate procedures should be in place to record, investigate and review complaints including potential quality defects, and if necessary, to effectively and promptly recall medicinal products for human or veterinary use and investigational medicinal products from the distribution network. Quality Risk Management principles should be applied to the investigation and assessment of quality defects and to the decision-making process in relation to product recalls and other risk-reducing actions. Guidance in relation to these principles is provided in Chapter 1.

All concerned competent authorities should be informed in case of a quality defect (faulty manufacture, product deterioration, detection of falsification, non-compliance with the marketing authorisation or product specification file, or any other serious quality problems) with a medicinal or investigational medicinal product which may result in the recall of the product or an abnormal restriction in the supply.

In case of outsourced activities, a contract should describe the role and responsibilities of the manufacturer, the Marketing Authorisation Holder and/or Sponsor and any other relevant third parties in relation to assessment, decision-making, and dissemination of information and implementation of risk-reducing actions relating to a defective product. Guidance in relation to contracts is provided in Chapter 7.

### **Personnel and Organisation**

8.1 Appropriately trained and experienced personnel should be responsible for managing complaint and quality defect investigations and for deciding the measures to be taken to manage any potential risk(s) presented by those issues, including recalls. These persons should be independent of the sales and marketing organisation, unless otherwise justified. If these persons do not include the Qualified Person who is involved in the certification for release of the concerned product, the latter should be made formally aware of any investigations, any risk-reducing actions and any recall operations, in a timely manner.

8.2 Sufficient personnel and resources should be made available for the handling, reviewing and investigation of complaints and quality defects and for implementing any risk-reducing actions. Sufficient personnel and resources should also be available for the management of interactions with competent authorities.

8.3 The use of inter-disciplinary teams should be considered, including appropriately trained Quality Management personnel.

8.4 In situations in which complaint and quality defect handling is managed centrally within an organisation, the relative roles and responsibilities of the concerned parties should be documented. Central management should not, however, result in delays in the investigation and management of the issue.

### **Procedures for handling and investigating complaints including possible quality defects**

8.5 There should be written procedures describing the actions to be taken upon receipt of a complaint. All complaints should be documented and assessed to establish if they represent a potential quality defect or other issue.

8.6 As all complaints received by a company may not represent actual quality defect issues, complaints which do not indicate a potential quality defect should be documented appropriately and communicated to the relevant group or person responsible for the investigation and management of complaints of that nature, such as suspected adverse events.

8.7 There should be procedures in place to facilitate a request to investigate the quality of a batch of a medicinal product to support an investigation into a reported suspected adverse event.

8.8 When a quality defect investigation is initiated, procedures should be in place to address at least the following:

- i. The description of the reported quality defect.
- ii. The determination of the extent of the quality defect. The checking or testing of reference and/or retention samples should be considered as part of this, and in certain cases, a review of the batch production record should be performed.
- iii. The need to request a sample of the defective product from the complainant and, where a sample is provided, the need for an appropriate evaluation to be carried out. The distribution information for the batch(es) in question. The assessment of the risk(s) posed by the quality defect.
- iv. The decision making process that is to be used concerning the potential need for risk-reducing actions to be taken in the distribution network, such as batch or product recalls, or other actions.
- v. The assessment of the impact that any recall action may have on the availability of the medicinal product to patients/animals in any affected market and the need to notify any such impacts to the relevant authorities.
- vi. The internal and external communications that should be made in relation to a quality defect and its investigation.
- vii. The identification of the potential root cause(s) of the quality defect.
- viii. The need for appropriate Corrective and Preventative Actions (CAPAs) to be identified and implemented for the issue, and for the assessment of the effectiveness of those CAPAs.

### **Investigation and Decision Making**

8.9 The information reported in relation to possible quality defects should be recorded, including all the original details. The validity and extent of all reported quality defects should be documented and assessed in accordance with quality risk management principles in order to support decisions regarding the degree of investigation and action taken.

8.10 If a quality defect is discovered or suspected in a batch, consideration should be given to checking other batches and in some cases other products, in order to determine whether they are also affected. In particular, other batches which may contain portions of the defective batch or defective components should be investigated.

8.11 Quality defect investigations should include a review of previous quality defect reports or any other relevant information for any indication of specific or recurring problems requiring attention and possibly further regulatory action.

8.12 The decisions that are made during and following quality defect investigations should reflect the level of risk that is presented by the quality defect as well as the seriousness of any non-compliance with respect to the requirements of the marketing authorisation/ product specification file or GMP. Such decisions should ensure that patient and animal safety is maintained in a timely manner, in a way that is commensurate with the level of risk that is presented by those issues.

8.13 As comprehensive information on the nature and extent of the quality defect may not always be available at the early stages of an investigation, the decision-making processes should still ensure that appropriate risk-reducing actions are taken at an appropriate time-point during such investigations. All the decisions and measures taken as a result of a quality defect should be documented.

8.14 Quality defects should be reported in a timely manner by the manufacturer to the Marketing Authorisation Holder/Sponsor and all concerned Competent Authorities in cases where the quality defect may result in the recall of the product or in an abnormal restriction in the supply of the product.

### **Root Cause Analysis and Corrective and Preventative Actions**

8.15 An appropriate level of root cause analysis work should be applied during the investigation of quality defects. In cases where the true root cause(s) of the quality defect cannot be determined, consideration should be given to identifying the most likely root cause(s) and to addressing those.

8.16 Special attention should be given to establishing whether a quality defect relates to falsification.

8.17 Where human error is suspected or identified as the cause of a quality defect, this should be formally justified and care should be exercised so as to ensure that process, procedural or system-based errors or problems are not overlooked, if present.

8.18 Appropriate corrective and/or preventative actions (CAPAs) should be identified and taken in response to a quality defect. The effectiveness of such actions should be monitored and assessed.

8.19 Quality defect records should be reviewed and trend analyses should be performed regularly for any indication of specific or recurring problems requiring attention.

## **Product Recalls and other potential risk-reducing actions**

8.20 There should be established written procedures, regularly reviewed and updated when necessary, in order to undertake any recall activity or implement any other risk-reducing actions.

8.21 Any retrieval of product from the distribution network as a result of a quality defect should be regarded and managed as a recall.

8.22 Recall operations should be capable of being initiated promptly and at any time. In certain cases recall operations may need to be initiated to protect public or animal health prior to establishing the root cause(s) and full extent of the quality defect

8.23 The batch/product distribution records should be readily available to the persons responsible for recalls, and should contain sufficient information on wholesalers and directly supplied customers (with addresses, phone and/or fax numbers inside and outside working hours, batches and amounts delivered), including those for exported products and medical samples.

8.24 In the case of investigational medicinal products, all trial sites should be identified and the countries of destination should be indicated. In the case of an investigational medicinal product for which a marketing authorisation has been issued, the manufacturer of the investigational medicinal product should, in cooperation with the sponsor, inform the marketing authorisation holder of any quality defect that could be related to the authorised medicinal product. The sponsor should implement a procedure for the rapid unblinding of blinded products, where this is necessary for a prompt recall. The sponsor should ensure that the procedure discloses the identity of the blinded product only in so far as is necessary.

8.25 Consideration should be given following consultation with the concerned Competent Authorities, as to how far into the distribution network a recall action should extend, taking into account the potential risk to public or animal health and any impact that the proposed recall action may have. The Competent Authority should also be informed in situations in which no recall action is being proposed for a defective batch because the batch has expired (such as with short shelf-life products.)

8.26 All concerned Competent Authorities should be informed in advance in cases where products are intended to be recalled. For very serious issue (i.e. those with the potential to seriously impact upon patient or animal health), rapid risk-reducing actions (such as a product recall) may have to be taken in advance of notifying the Competent Authorities. Wherever possible, attempts should be made to agree these in advance of their execution with the concerned Competent Authorities

8.27 It should also be considered whether the proposed recall action may affect different markets in different ways, and if this is the case, appropriate market-specific risk-reducing actions should be developed and discussed with the concerned competent authorities. The risk of shortage of an essential medicinal product which has no authorised alternative should be considered before deciding on a risk-reducing action such as a recall. Any decisions not to execute a risk-reducing action which would otherwise be required should be agreed with the competent authority in advance.

8.28 Recalled products should be identified and stored separately in a secure area while

awaiting a decision on their fate. A formal disposition of all recalled batches should be made and documented and the rationale for the disposition of recalled products (or any reworked versions of them) should be documented and discussed with the relevant competent authority. The extent of shelf-life remaining for any reworked batches that are being considered for placement onto the market should also be considered.

8.29 The progress of the recall process should be recorded and a final report issued, including a reconciliation between the delivered and recovered quantities of the concerned products/batches.

8.30 The effectiveness of the arrangements in place for recalls should be periodically evaluated to confirm that they remain robust and fit for use. Such evaluations should extend to both within office-hour situations as well as out-of-office hour situations and, when performing such evaluations, consideration should be given as to whether mock-recall actions should be performed. This evaluation should be documented and justified.

8.31 In addition to recalls, there are other potential risk-reducing actions that may be considered in order to manage the risks presented by quality defects. Such actions may include the issuance of cautionary communications to healthcare professionals in relation to their use of a batch that is potentially defective. These should be considered on a case-by-case basis and discussed with the concerned competent authorities.