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Good Manufacturing Practice
Medicinal Products for Human and Veterinary Use

Chapter 5: Production

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. 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 **for public consultation**

Deadline for public consultation: 28 February 2011

Reasons for changes: changes have been proposed to sections 25 and 26 on the qualification of suppliers of starting material in order to reflect the legal obligation of manufacturing authorisation holders to ensure that active substances are produced in accordance with GMP. Supply chain traceability for starting materials is also introduced in sections 26 and 27. A new section, 31, is proposed in order to clarify and harmonise expectations of manufacturers regarding the testing of starting materials. Further work on chapter 5 is ongoing, affecting section 19, as referred to in the Concept Papers published by EMA in February 2005. EMA also published progress reports on this work in February 2008 and December 2009.

Commission Européenne, B-1049 Bruxelles / Europese Commissie,
B-1049 Brussel - Belgium
Telephone: (32-2) 299 11 11

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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.

5.17 Normally, the production of non-medicinal products should be avoided in areas and with the equipment destined for the production of medicinal products.

Prevention of cross-contamination in production

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 or organisms from materials and 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. Amongst the most hazardous contaminants are highly sensitising materials, biological preparations containing living organisms, certain hormones, cytotoxics, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection, those given in large doses and/or over a long time.

5.19 Cross-contamination should be avoided by appropriate technical or organisational measures, for example:

a) Production in segregated areas (required for products such as penicillins, live vaccines, live bacterial preparations and some other biologicals), or by campaign (separation in time) followed by appropriate cleaning;

b) Providing appropriate air-locks and air extraction;

c) Minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;

d) Keeping protective clothing inside areas where products with special risk of cross contamination are processed;

e) Using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination;

f) Using “closed systems” of production;

g) Testing for residues and use of cleaning status labels on equipment.

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

Validation

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

5.22 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.

5.23 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.

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

Starting materials

5.25 Starting materials should only be purchased from manufacturers, importers or distributors of active substances approved by the manufacturers of medicinal products, named in the relevant specification and, where possible, directly from the manufacturer of the starting material. Purchase of starting materials should be controlled by written procedures. The supply chain of each starting materials should be known and be documented.

It is recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is of benefit that all aspects of the production and control of the starting material in question, including handling, labelling, packaging and distribution requirements, as well as complaints and rejection procedures are discussed with the manufacturer and supplier, and that the outcome of these discussions are documented.

5.26 The selection, including qualification and approval of suppliers, and the purchase of starting materials is an important operation which should involve staff who have a particular and thorough knowledge of the suppliers and the associated risks involved in that starting material’s supply chain. Procedures for the assessment and purchase and acceptance of starting materials, including critical packaging materials should be documented as part of the quality management system. The approval of suppliers of starting materials should be

controlled by QC and production. Suppliers of active substances and, certain excipients considered to be high risk materials used as starting materials, should be periodically audited to confirm that they comply with current GMP requirements and that supply chain traceability[1] of the starting material is being maintained. The findings from each audit should be documented, and audit reports should be available for review by Inspectors.

5.27 For each delivery, the containers should be checked for integrity of package and seal and for correspondence between the delivery note and the supplier's labels. Verification of the supply chain traceability should also be established and documented.

5.28 If one material delivery is made up of different batches, each batch must be considered as separate for sampling, testing and release.

5.29 Starting materials in the storage area should be appropriately labelled (see Chapter 5, section 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.

5.30 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, section 13).

5.31 Manufacturers of the medicinal product are responsible for any testing of starting materials as described in the marketing authorisation dossier. Manufacturers of finished product can subcontract the testing of starting materials described in the marketing authorisation dossier to the approved starting material manufacturer but must, as a minimum, perform a confirmation of identity themselves.

The following requirements should be fulfilled when introducing subcontracting of partial or full testing:

- A formal agreement should be signed 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.

- 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 GMP and the specifications and testing methods described in the Marketing Authorisation.

[1] A record of where each active substance (including its critical starting materials) is manufactured, propagated, processed and handled prior to its use in the manufacture of a medicinal product. The record should include the names and addresses (including reference to the DUNS number) of each manufacturer, distributor, trader/broker and shipper involved in this part of the supply chain.

- 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,

- Full analyses should be conducted on at least three different batches before reducing in-house testing. As a minimum, 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 its reliability. Should this testing identify discrepancies then the acceptance of certificates of analysis from the supplier should be discontinued until investigations are completed.

Notes:

1. The same requirements apply to packaging materials as stated in GMP part I, 5.40.
2. Identity testing of starting materials should be performed according to the methods and the specifications of the relevant Marketing Authorisation dossier.

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 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.

5.34 Each dispensed material and its weight or volume should be independently checked and the check recorded.

5.35 Materials dispensed for each batch should be kept together and conspicuously labelled as such.

Processing operations: intermediate and bulk products

5.36 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.

5.37 Intermediate and bulk products should be kept under appropriate conditions.

5.38 Critical processes should be validated (see "VALIDATION" in this Chapter).

5.39 Any necessary in-process controls and environmental controls should be carried out and recorded.

5.40 Any significant deviation from the expected yield should be recorded and investigated.

Packaging materials

5.41 The purchase, handling and control of primary and printed packaging materials shall be accorded attention similar to that given to starting materials.

5.42 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.

5.43 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.

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

Packaging operations

5.45 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.

5.46 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.

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

5.48 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.

5.49 Containers for filling should be clean before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.

5.50 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.

5.51 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.

5.52 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.

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

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

5.55 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.

5.56 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.

5.57 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.

5.58 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

5.59 Finished products should be held in quarantine until their final release under conditions established by the manufacturer.

5.60 The evaluation of finished products and documentation necessary before release of product for sale is described in Chapter 6 (Quality Control).

5.61 After release, finished products should be stored as usable stock under conditions established by the manufacturer.

Rejected, recovered and returned materials

5.62 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.

5.63 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. Records should be kept of the reprocessing.

5.64 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.

5.65 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.

5.66 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.