

# 2.

## WHO good manufacturing practices: starting materials

### Active pharmaceutical ingredients (bulk drug substances)<sup>1,2</sup>

Explanation	58
General considerations	58
Personnel	59
Premises	60
Equipment	60
Sanitation	61
Documentation	61
Retention of records and reference samples	63
Production	63

### Explanation

Since there are fundamental distinctions between the production of bulk active pharmaceutical ingredients and the formulation of finished pharmaceutical products, the strict application of GMP as set forth in the main part of this guide is not always practical or necessary. The present supplementary guidelines outline procedures and practices that manufacturers should employ to ensure that the methods, facilities, and controls used for the production of active pharmaceutical ingredients are operated or managed so that such products have the quality and purity appropriate for their use in finished pharmaceutical products.

### General considerations

1 In the manufacture of active pharmaceutical ingredients, overall control is essential to ensure high quality. Haphazard operations cannot be permitted in the

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<sup>1</sup> Good manufacturing practices for pharmaceutical products, Part Three, section 18. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992: 72–79 (WHO Technical Report Series, No. 823).

<sup>2</sup> Introductory note, General considerations main principles and Glossary of Good manufacturing practices for pharmaceutical products are reproduced elsewhere in this volume (see pp. 8–57, 86–102).

manufacture of substances that may be used to save life or to restore or promote health.

2 Recommended practices for the manufacture of active pharmaceutical ingredients are set out below. Adherence to these practices, complementing the various control tests carried out from the beginning to the end of the production cycle, will contribute substantially to the production of consistently uniform batches of high-quality active pharmaceutical ingredients.

3 The manufacturer must assume responsibility for the quality of the active pharmaceutical ingredients produced. The manufacturer alone can avoid mistakes and prevent mishaps by exercising adequate care in both production and control procedures. Full evidence of compliance with GMP should be given from the step from which the processes or the starting materials used have a critical influence on the quality of the active pharmaceutical ingredient. This step should be determined in each individual case by agreement between the competent authority and the manufacturer.

4 The good practices outlined below should be considered general guides; whenever necessary, they may be adapted to meet individual needs provided the established standards of quality of the active pharmaceutical ingredients are still achieved. The good practices are intended to apply to the manufacturing processes (including packaging and labelling) used in the production of active pharmaceutical ingredients.

5 Sometimes several firms cooperate in the production (including packaging and labelling) of an active pharmaceutical ingredient. It may also happen that a finished, packed, and labelled active pharmaceutical ingredient is repacked and/or relabelled and given a new designation. Since such procedures constitute part of a manufacturing operation, they should be subject to the relevant guidelines set out below.

6 The practices outlined below are intended to apply to active pharmaceutical ingredients for both human and veterinary preparations.

## **Personnel**

7 Each firm should employ personnel with the necessary qualifications and competence for the production and quality control of active pharmaceutical ingredients. There should be an adequate number of staff with appropriate education, technical knowledge, and practical experience related to the job they perform.

8 The firm should have a defined organization represented in a chart. Individual responsibilities should be laid down in written instructions, to ensure that there are no gaps or overlaps. The responsibilities placed on any one individual should not be so extensive as to incur any risk to quality.

9 Staff at all levels should be adequately trained for the tasks and responsibilities assigned to them.

10 Measures should be taken to ensure that no person affected by a disease in a communicable form or having open lesions on the exposed surface of the body is engaged in any production step involving direct contact with the active pharmaceutical ingredients.

## **Premises**

11 Premises, including areas containing open tanks, should be of suitable construction. They should provide a suitable environment for manufacturing operations and should be adequately adapted to and of a sufficient size for their intended use. The premises should not contribute to actual or potential mix-ups or contamination of the active pharmaceutical ingredients. The arrangement should provide for a logical work flow.

12 For special purposes, such as the production of sterile products and of certain antibiotics, hormones, and cytostatic substances, separate specifically designed enclosed areas with completely separate air-handling systems should be provided.

13 To maintain hygienic working conditions, the premises should include facilities for changing clothes, washing, and toilet purposes as well as for eating, drinking, and smoking.

## **Equipment**

14 Manufacturing equipment should be designed, constructed, located, and maintained in such a way as to:

- (a) be suitable for its intended use;
- (b) facilitate thorough cleaning;
- (c) minimize the risk of contamination of products and containers during production; and
- (d) facilitate efficient and, if applicable, validated and reliable operation.

15 Production and testing equipment should be cleaned, sterilized when necessary, used, and maintained in accordance with specific written instructions. Before production of another product is started, multipurpose equipment used should be thoroughly cleaned and checked for cleanliness. Appropriate records of such procedures should be maintained.

16 If necessary, equipment used for production and testing should have been shown to be capable of carrying out the processes for which it is intended.

17 Process-monitoring systems should be available where necessary. Measuring, recording, and control equipment should be calibrated and checked at suitable intervals by appropriate methods. Appropriate records of such tests should be maintained.

18 Defective equipment should be labelled immediately as defective and repaired or removed as soon as possible. Technical maintenance and repair should be documented.

## **Sanitation**

19 Written sanitation programmes should be available. These should include validated cleaning procedures for premises and equipment, a quality standard for water, instructions for hygiene when manufacturing and handling goods, and instructions relating to the health, hygienic practices, and clothing of personnel and the disposal procedures for waste materials and unusable residues.

20 These programmes should be implemented; they should regularly be brought to the attention of the personnel involved and emphasized during continued staff training.

21 Protective garments and other protective items appropriate to the processes being carried out should be worn.

22 Eating, smoking, and unhygienic practices should not be permitted in manufacturing areas.

## **Documentation**

### Master formulae

23 Written instructions covering each stage of production, storage, and quality control should be available, and they should be updated whenever necessary.

24 There should be a master formula setting out in writing the starting materials and packaging materials (quality and quantity), as well as detailed production and quality control procedures for each active pharmaceutical ingredient. Wherever possible, the master formula should be prepared for standard batch sizes.

25 Competent persons experienced in production and quality control should be responsible for the content and distribution within the firm of instructions and master formulae. These should be duly signed and dated.

26 Outdated master formulae should be withdrawn but retained for reference. Copies of the master formula should be prepared in a manner that will eliminate any possibility of transcription error.

27 In certain circumstances, for example in the first production runs following pilot development, the master formula might need to be amended. Any amendments must be formally authorized and signed by competent person(s). The amended document should be replaced at the earliest opportunity by a newly prepared master formula.

### Batch documentation

28 A batch manufacturing record should be completed during the production of each batch of intermediate products and of active pharmaceutical ingredients. It should contain the relevant parts of the master formula and should include the following:

- (a) the name of the product (if applicable, the International Nonproprietary Name) or stage and the size and number of the batch;
- (b) the dates of the different stages of production;
- (c) production details, including reference to the main equipment used and yields;
- (d) the batch or reference number (or analytical control number), if any, of starting materials used in the production;
- (e) a record of the in-process controls followed and the results obtained;
- (f) details of, and signed authorization for, any deviation from the master formula (any unplanned deviation being subject to investigation in relation to product quality);
- (g) any recovered materials, and procedures applied;
- (h) the initials of the operators and signature of the person responsible for the production operations and the date of signature;
- (i) all analytical records relating to the batch, or a reference that will permit their retrieval;
- (j) a decision for the release or rejection of the batch with the date and signature of the person responsible for the decision;
- (k) the production record review (see section 17.21).

29 Where circumstances require the use of contract production and control facilities, this fact should be stated in the batch record.

30 Data may be recorded by electronic data-processing systems or by photographic or other reliable means. Master formulae and detailed standard operating procedures relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data-processing methods, only authorized persons should be able to enter or modify data in the computer, and there should be a record of changes and deletions; access should be restricted by passwords or other means, and the entry of critical data should be independently checked. Batch records electronically stored should be protected by back-up transfer on magnetic tape,

microfilm, paper print-outs, or other means. It is particularly important that, during the period of retention, the data are readily available.

## **Retention of records and reference samples**

31 Records should be kept in such a way that activities concerning the production and quality control of active pharmaceutical ingredients are traceable.

32 Records and reference samples of the active pharmaceutical ingredients, and, where necessary, of intermediate products, should be retained at least one year beyond the expiry date of the finished product or for a specified period if there is no expiry date.

## **Production**

### Processing procedures

33 Processing should be carried out in accordance with the master formula.

34 Steps that are critical for the quality of the active pharmaceutical ingredient should be defined and the procedures applied should be validated.

35 Processing should be supervised and performed by competent persons.

36 During processing, vessels, containers, and significant equipment should be unambiguously labelled or identified with the name of the product and the batch number.

37 Information on the daily activities in each processing department should be available in addition to the batch documentation.

### Starting materials

38 Starting materials should be received, quarantined, sampled, identified, examined for compliance with established specifications, released or rejected, stored, labelled, and dispensed in accordance with written instructions.

39 Some starting materials may not be tested for compliance because of the hazards involved (e.g., phosphorus pentachloride and dimethyl sulfate). This is acceptable when a batch certificate of analysis is available from the vendor and when there is a reason based on safety or other valid considerations.

### Intermediate products

40 Intermediate products should, where necessary, be tested in accordance with the specifications and should be conspicuously labelled/identified and properly stored.

## Active pharmaceutical ingredients

41 Each batch of finished active pharmaceutical ingredient must meet established specifications for quality, purity, identity, and potency, including, where applicable, specifications for tests and limits for residues of solvents and other reactants.

42 For the production of sterile active pharmaceutical ingredients, the first section of chapter 3 (“Sterile pharmaceutical products”) may be applicable to the steps at which the process may have a critical influence on the quality attributes of the finished pharmaceutical product.

## Packaging

43 Care should be exercised when packaging materials are selected for active pharmaceutical ingredients. The materials should have no detrimental effect on the substance, and should give adequate protection against external influences and potential contamination. Suitable written specifications should be available.

44 Attention should be directed at all stages to the prevention of packaging errors. Sound procedures must be employed to protect the quality of the product when it is packaged and to ensure that the correct labels are applied to the containers.

45 The containers should be conspicuously marked with the following information:

- (a) the name of the product;
- (b) its quality, if specified;
- (c) the batch number;
- (d) the expiry or retest date, if specified;
- (e) warnings, if required;
- (f) storage conditions, if specified; and
- (g) the names of the manufacturer and the supplier.

## Quality control

46 Every manufacturer should have an independent quality control unit, the head of which is directly responsible to the management of the firm. The principal duties of the quality control unit are listed below.

- (a) It should approve:
  - (i) specifications and testing methods for starting materials, intermediate products and, if required, packaging materials and active pharmaceutical ingredients;

- (ii) sampling procedures;
  - (iii) instructions regarding sanitation and hygiene;
  - (iv) reprocessing procedures for rejected batches or recovered materials;
  - (v) other instructions related to the quality of the product.
- (b) It should be responsible for the release or rejection of starting materials, active pharmaceutical ingredients, packaging materials, and, if required, intermediate products.
  - (c) It should ensure that the stability of active pharmaceutical ingredients is monitored.
  - (d) It should be responsible for the investigation of complaints related to the quality of active pharmaceutical ingredients.

47 Every manufacturer should have access to a control laboratory. The laboratory should be staffed and fully equipped for performing all quality control tests required. The tests should be performed in accordance with written and validated procedures. Instruments should be calibrated at suitable intervals and reagents should be of appropriate quality.

48 Where circumstances require the use of outside laboratories, this fact should be stated in the analytical records.

### Stability studies

49 A written stability-testing programme should be established for active pharmaceutical ingredients. Stability-indicating methods should be used.

50 Samples should be stored in suitable containers and in simulated market containers at room temperature or the recommended temperature and under stress conditions.

51 Expiry dates do not usually need to be set for active pharmaceutical ingredients. If testing does not indicate a reasonable shelf-life, e.g. two years or more under anticipated storage conditions, then the product can be labelled with an appropriate arbitrary expiry date and should be retested on or before that date.

### Self-inspection and quality audits

52 In order to maintain strict adherence to GMP and to all manufacturing procedures and prescribed controls, it is advisable for a firm to designate an expert or a team of experts to conduct regular independent inspections of its overall production and control procedures. Such experts should be as independent as possible in their inspection of production and control procedures.

53 Self-inspections and audits (see section 9) should be recorded.

## Storage

54 Active pharmaceutical ingredients should be stored under conditions established by the manufacturer on the basis of stability studies.

55 Records should be maintained on the distribution of each batch of an active pharmaceutical ingredient in order to facilitate the recall of the batch if necessary, according to written procedures.

## Complaints and defects

56 The manufacturer should maintain written instructions for dealing with complaints and defects concerning the quality of active pharmaceutical ingredients.

57 All necessary action should be taken promptly, the complaints thoroughly investigated, and all facts recorded.

58 The manufacturer should have a system to allow review of all products that may have been affected by a repetitive error or a failure in the procedures of the firm.

## Rejected materials

59 The manufacturer should maintain written instructions concerning the handling of rejected materials, whether starting materials, intermediate products, packaging materials, or active pharmaceutical ingredients. Rejected materials should be conspicuously identified as such and stored in a controlled manner pending destruction, reprocessing, or return to the supplier.

## Pharmaceutical excipients<sup>1</sup>

1. General considerations	67
2. Glossary	70
3. Self-inspection and quality audits	71
4. Equipment	72
4.1 Use of equipment	72
4.2 Cleaning programme	72
4.2.1 Detailed cleaning procedure	73
4.2.2 Sampling plan	73
4.2.3 Analytical methods/cleaning limits	73

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<sup>1</sup> Good manufacturing practices: supplementary guidelines for the manufacture of pharmaceutical excipients. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fifth report.* Geneva, World Health Organization, 1999, Annex 5 (WHO Technical Report Series, No. 885).

5. Materials	73
5.1 General	73
5.2 Starting materials	74
5.3 Rejected and recovered materials	74
5.4 Returned excipients	75
5.5 Storage practices	75
6. Documentation	75
6.1 General	75
6.2 Specifications	76
6.3 Batch production records	76
6.4 Other documents	77
7. Good practices in production and quality control	77
7.1 Change control and process validation	77
7.2 Good practices in production	78
7.2.1 Prevention of cross-contamination	78
7.2.2 In-process blending/mixing	79
7.2.3 Control of microbial contamination	80
7.2.4 Water systems/water quality	81
7.2.5 Packaging operations	82
7.2.6 Delivery	82
7.3 Good practices in quality control	82
7.3.1 General	82
7.3.2 Control of starting materials	82
7.3.3 In-process testing	83
7.3.4 Quality records and retention samples	83
7.3.5 Stability studies	83
7.3.6 Expiry/re-evaluation dating	84
7.3.7 Calibration of measuring and test equipment	84

## 1. General considerations

These guidelines, which focus on aspects of good manufacturing practices (GMP) specific for pharmaceutical excipients, supplement the general GMP guidelines for pharmaceutical products published by WHO.<sup>1</sup> They also incorporate some of the concepts for quality management systems determined by the International Organization for Standardization (ISO).

Excipients significantly affect the finished product quality, in some cases making up almost the entire formulation. Many pharmaceutical excipients are

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<sup>1</sup> Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-second report*. Geneva, World Health Organization, 2003, Annex 4 (WHO Technical Report Series, No. 908). In this volume, see pp. 7–58.

used in much greater quantities in other industries, such as the food, cosmetic or industrial chemical industry. Consistency and rigour of product specifications may not be as critical in these industries as they are for pharmaceuticals, and many of the excipients used are highly variable. Therefore, a programme must be in place which will monitor these excipients and provide the necessary assurance that they meet the quality parameters for pharmaceutical manufacturing processes. The purpose of this document is to lay out some criteria which may be used to achieve this level of assurance.

The formulator of the finished dosage form is highly dependent on the excipient manufacturer to provide bulk substances that are uniform in chemical and physical characteristics. This is particularly important in the product approval process, where bioequivalence comparisons are made between clinical bioequivalence (“biobatch”) production and commercial scale-up batches. To provide adequate assurance of drug product performance *in vivo*, the excipient used to manufacture commercial batches should not differ significantly from that used in biobatches. Where significant differences may be expected, additional testing by the finished dosage manufacturer may be required to establish the bioequivalence of the finished product. It remains equally important to ensure that the bioequivalence of subsequent, post-approval commercial batches of drug products is not adversely affected over time.

In general, excipients are used as purchased, with no further refinement or purification. Consequently, impurities present in the excipient will be carried over to the finished dosage form. While dosage form manufacturers may have a limited control over excipient quality (i.e. by obtaining certificates of analysis and testing representative samples), the excipient manufacturer has greater control over physical characteristics, quality, and the presence of trace-level impurities in the excipient. The excipient manufacturer should perform periodic performance trend analyses of processes, and the purchaser of the material should also maintain a trend analysis of all testing done on the excipient upon receipt.

In the manufacture of excipients, the environmental conditions, equipment and operational techniques employed reflect the chemical industry rather than the finished drug manufacturing industry. In some processes chemical and biochemical mechanisms have not been fully characterized; therefore, the methods and procedures for materials accountability will often differ from those applicable to the manufacture of finished dosage forms. Many chemical processes are performed in closed systems that tend to provide protection against contamination, even when the reaction vessels are not enclosed in buildings. However, this does not preclude the introduction of contaminants from equipment, materials used to protect equipment, corrosion, cleaning and personnel.

Some excipient manufacturing processes may require observance of GMP applicable to finished drug products or bulk active ingredients because of the excipient’s intended use. However, such observance is neither feasible nor necessary in many processes, particularly during the early processing steps. The

requirements increase as the process progresses. At some logical processing step, usually well before the final finishing operation, appropriate GMP should be imposed and maintained throughout the remainder of the process. To determine the processing step at which these GMP should be implemented, good judgement and a thorough knowledge of the process are required. A detailed process flow should identify the unit operations, equipment used, stages at which various substances are added, key steps in the process, critical parameters (time, temperature, pressure, etc.) and monitoring points.

An excipient manufacturer should be able to identify critical or key points in the process where selective intermediate sampling and testing is necessary in order to monitor process performance. Towards the end of the process, the records should be increasingly thorough.

Significant processing steps, required to produce an excipient that meets the established physical and chemical criteria, should be identified by the excipient manufacturer. These steps can involve a number of unit operations or unit processes. Unit operations include physical processing steps involving energy transfer where there is no chemical change of the molecule. Unit processes are those processing steps where the molecule undergoes a chemical change.

Significant processing steps include but are not limited to the following:

- Phase changes involving either the desired molecule, a solvent, inert carrier or vehicle (e.g. dissolution, crystallization, evaporation, drying, sublimation, distillation or absorption).
- Phase separation (e.g. filtration or centrifugation).
- Chemical changes involving the desired molecule (e.g. removal or addition of water of hydration, acetylation, formation of a salt).
- Adjustments of the solution containing the molecule (e.g. adjustment of pH).
- Precision measurement of added excipient components, in-process solutions, recycled materials (e.g. weighing, volumetric measuring).
- Mixing of multiple components.
- Changes that occur in surface area, particle size or batch uniformity (e.g. milling, agglomeration, blending).

Automated process controls and processing equipment are more likely to be used in an excipient plant than in a plant manufacturing finished dosage forms. Use of automated equipment is appropriate when adequate inspection, calibration, and maintenance procedures are performed. Production equipment and operations will vary depending on the type of excipient being produced, the scale of production, and the type of operation (i.e. batch versus continuous).

ISO "certification" for excipient manufacture is increasingly being required by final dosage formulators in the USA, Europe and Japan. Compliance to the International Standards of ISO 9000 series, in particular to ISO 9002, can confer greater acceptability of a supplier's excipients in world markets. There is additional value to applying the principles of ISO 9000 to excipient manufacture, since quality system measures enhance GMP. Such ISO considerations as con-

formance to specific customer requirements, purchase of raw materials and statistical techniques benefit both the excipient customer and the manufacturer, and strengthen the relationship between the two.

It is therefore recommended that excipient manufacturers establish and implement a formal company-wide quality policy. Management should be committed to this policy and should appoint appropriate company personnel to be responsible for coordination and implementation of the quality system. Management should participate in the development of the company's quality policy and provide the resources necessary for development, maintenance and periodic review of such a policy and quality system. Any significant changes in the processes should be validated with respect to excipient performance. It is recommended that all pharmaceutical manufacturers and also local agents should be informed of these changes. Ideally, excipient manufacturers should not subcontract any part of their process without the explicit knowledge of the pharmaceutical manufacturer.

Safe handling instructions should be provided by the excipient manufacturer to ensure that the purchaser is adequately equipped to handle the material. This should include information on the material's toxicity and the measurements to be taken upon accidental exposure. The equipment requirements for proper handling of the material should also be established.

## 2. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

### *commingling*

The blending of carry-over material from one grade of an excipient with another, usually due to a continuous process.

### *drug master file*<sup>1</sup>

Detailed information concerning a specific facility, process or product submitted to the drug regulatory authority, intended for incorporation into the application for marketing authorization.

### *model product*

A product which simulates a group of similar products.

### *mother liquor*

A concentrated solution from which the product is obtained by evaporation, freezing, and/or crystallization.

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<sup>1</sup> This term appears to be specific to United States regulations.

*pharmaceutical excipients*

Substances, other than the active ingredient, which have been appropriately evaluated for safety and are included in a drug delivery system to:

- aid in the processing of the drug delivery system during its manufacture;
- protect, support or enhance stability, bioavailability, or patient acceptability;
- assist in product identification; or
- enhance any other attribute of the overall safety and effectiveness of the drug during storage or use.

### 3. Self-inspection and quality audits

An inspection team consisting of appropriate personnel (e.g. auditors, engineers, laboratory analysts, purchasing agents, computer experts) should participate in inspections. The operational limitations and validation of the critical processing steps of a production process should be examined, to make sure that the manufacturer is taking adequate steps to check that the process works consistently.

The excipient's end-use should be identified and considered during inspection of excipient manufacturers. It is particularly important to know whether the excipient is a direct or indirect component of a drug dosage form; whether the excipient will be used in the preparation of a sterile dosage form; and whether the excipient is presented as pyrogen/endotoxin free. The excipient manufacturer is responsible for ensuring that excipients are pyrogen free if the manufacturer makes such a representation in specifications, labels or a drug master file.

A good starting point for an excipient plant inspection is a review of the following areas:

- Non-conformance, such as the rejection of a batch not complying with specifications, return of a product by a customer, or recall of a product. The cause of non-conformance should have been determined by the manufacturer, a report of the investigation prepared, and subsequent corrective action initiated and documented. Records and documents should be reviewed to ensure that such non-conformance is not the result of a poorly developed or inconsistent process.
- Complaint files. Customers may report some aspects of product attributes that are not entirely suitable for their use. These may be caused by impurities or inconsistencies in the excipient manufacturing process.
- Change control documentation.
- Master formula and batch production records. Frequent revisions may reveal problems in the production process.
- Specifications for the presence of unreacted intermediates and solvent residues in the finished excipient.
- Storage areas for rejected products.

In evaluating the adequacy of measures taken to preclude contamination of materials in the process, it is appropriate to consider the following factors:

- Type of system (e.g. open or closed). “Closed” systems in chemical plants are often not closed when they are being charged and/or when the final product is being removed. Also, the same reaction vessels are sometimes used for different reactions.
- Form of the material (e.g. wet or dry).
- Stage of processing and use of the equipment and/or area (e.g. multipurpose or dedicated).

Other factors that should be considered in evaluating an excipient plant are:

- Degree of exposure of the material to adverse environmental conditions.
- Relative ease and thoroughness of clean-up.
- Sterile versus non-sterile operations.

## 4. Equipment

### 4.1 Use of equipment

Many excipients are produced using multipurpose equipment. Fermentation tanks, reactors, driers, grinders, centrifuges and other pieces of equipment are readily used or adapted for a variety of products. With few exceptions such multiple usage is satisfactory provided the equipment can be adequately cleaned according to written procedures. Equipment that contains tarry or gummy residues that cannot be removed easily should be dedicated for use with these products only.

Some fermentation tanks, reaction vessels, and other equipment are not situated within a building and a considerable amount of processing occurs out of doors. Such processing is acceptable provided it occurs in a closed system.

Where temperature control is important, temperature recording devices should be used, with recording charts kept as part of the batch record.

### 4.2 Cleaning programme

Where multipurpose equipment is in use, it is important to be able to determine previous usage when investigating cross-contamination or the possibility of such contamination. An equipment cleaning and use log, while desirable and perhaps preferable, is not the only method of determining prior use. Any documentation system which clearly identifies the previous batch and shows that the equipment was cleaned is acceptable. For operations where multiple grades of the same chemical entity are processed, there must be documentation showing that the previous grade was removed. Validation data must exist to prove acceptability of the cleaning procedure.

Cleaning of multiple-use equipment should be confirmed. The manufacturer should determine the effectiveness of the cleaning procedure for each excipient or intermediate chemical used in that particular piece of equipment. The validation data required depend on the types of materials being made in the multiple-use equipment and the impact of trace contaminants on drug safety and performance. Validation data should verify that the cleaning process has removed residues to an acceptable level.

As an example, an equipment cleaning programme may include, but is not limited to, the following:

#### **4.2.1 Detailed cleaning procedure**

There should be a written equipment cleaning procedure that provides details of what should be done and which cleaning materials should be used. Some manufacturers list the specific solvents used for each excipient and intermediate.

#### **4.2.2 Sampling plan**

There should be some periodic testing after cleaning, to ensure that the surface has been cleaned to the required level. One common method is to analyse the final rinse water or solvent for the presence of the substance last used in that piece of equipment. In some cases, visual inspections may be appropriate. A specific analytical method to determine residual substances may not always be available, but is preferred. The need for an analytical method would be based on the potential adverse effect on product quality, performance or safety. When safety is a concern, there should be a specific analytical determination for a residual substance.

#### **4.2.3 Analytical methods/cleaning limits**

The toxicity of the residual materials should be considered when deciding on the appropriate analytical method and the residual cleaning limits. The residue limits established for each piece of apparatus should be practical, achievable and verifiable. The manufacturer should be able to show, with supporting data, that the residual level permitted is scientifically based. Another factor to consider is the possible non-uniformity of the residue. The level of residue found by random sampling, such as taking a swab from a limited area on a piece of equipment, does not necessarily represent the highest level of contamination.

## **5. Materials**

### **5.1 General**

In the case of labile products that may be sensitive to environmental factors such as air, light, water, heat or cold, appropriate manufacturing and storage conditions must be used to ensure product quality throughout the process.

## 5.2 Starting materials

The excipient manufacturer should verify that the supplier of starting materials and components can meet the agreed-upon requirements. This may require periodic audits of the vendor's plant if necessary. Purchasing agreements should contain data clearly describing the product ordered including, where applicable, the following:

- The name, type, class, style, grade, item code numbers or other precise identification as appropriate.
- Drawings, process requirements, inspection instructions and other relevant technical data, including requirements for approval or verification of product, procedures, process equipment and personnel.

Starting materials, including solvents and recovered solvents, are sometimes stored in silos or other large containers, making precise separation of batches difficult. Usage of such materials should be demonstrated, via inventory or other records, with reasonable accuracy.

When purchased and recovered solvents are commingled, the suitability of the recovered solvent must be demonstrated through either validation or actual testing. The purchased materials should comply with existing specifications.

Outdoor storage of starting materials (e.g. acids, other corrosive substances, explosive materials) is acceptable if the containers give suitable protection to their contents, identifying labels remain legible and containers are adequately cleaned prior to opening and use.

## 5.3 Rejected and recovered materials

Any starting material or intermediate or finished excipient not complying with specifications must be clearly identified and segregated to prevent inadvertent use or release for sale. A record of non-compliance should be maintained. All cases of non-compliance should be investigated to identify the root cause.

These materials may be:

- reprocessed/reworked to meet the specified requirements;
- regraded for alternative applications; or
- rejected or scrapped.

Occasional reprocessing/reworking of an excipient may be acceptable. However, relying on the final testing only of the reprocessed excipient to demonstrate compliance to specification is not acceptable. The quality of the reprocessed material must be evaluated and documented showing adequate investigation and demonstrating that the reprocessed excipient is at least equivalent to other acceptable excipients. When reprocessing has to be done frequently, it may be an indication that the process, work instruction or training is inadequate and needs to be adjusted or reinforced.

## 5.4 Returned excipients

Returned excipients should be identified as such and kept. If the conditions under which the products have been stored and shipped or if the condition of the container itself casts doubt on the safety, quality or purity of the excipient, the product should be destroyed, unless thorough examination, testing, or other investigation shows that the product meets the appropriate predefined standards. If returned excipient containers are reused, all previous labelling should be removed or defaced. If the containers are used repeatedly solely for the same excipient, all previous batch numbers, or the entire label, should be removed or completely obliterated.

## 5.5 Storage practices

Pharmaceutical excipients should be stored under conditions established by the manufacturer on the basis of stability data. Records should be kept of the distribution of each batch of pharmaceutical excipient, to facilitate the recall of the batch if necessary, according to written procedures.

# 6. Documentation

## 6.1 General

The excipient manufacturer should have a system to cover all documents and data that relate to the requirements of the quality system. Documents, and subsequent changes to the documents, should be reviewed and approved by designated personnel before being issued to the appropriate areas identified in the documents. A record should be kept of where the documents are located.

The following minimal requirements for documentation should be applied:

- To assign a unique batch number to the excipient to be released and/or certified.
- To prepare a batch record.
- To demonstrate that the batch has been prepared under GMP conditions from the processing point at which excipient GMP have been applied.
- To demonstrate that the batch is homogeneous within the manufacturer's specifications. This does not require a final blending of continuous process material, if process controls can demonstrate compliance with specifications throughout the batch.
- To demonstrate that the batch has not been commingled with material from other batches for the purpose of either hiding or diluting an adulterated substance.
- To demonstrate that the batch has been sampled in accordance with a sampling plan that ensures a representative sample of the batch is taken.

- To demonstrate that the batch has been analysed using scientifically established tests and methods designed to ensure that the product meets accepted standards and specifications for quality, identity and purity.
- To demonstrate that the batch has stability data to support the intended period of use; these data can be obtained from actual studies on the specific excipient or from applicable “model product” stability studies that can reasonably be expected to simulate the performance of the excipient.

## 6.2 Specifications

Starting material specifications should be organized to separate those tests that are routine from those that are performed infrequently or only for new suppliers. Relevant pharmacopoeial monographs, when available, provide a basis for the development of internal manufacturer’s specifications.

A positive identification test uniquely applicable to the excipients should be established through analytical technology, such as infrared spectrophotometry and chromatography.

It is important that manufacturers identify and set appropriate limits for impurities. These limits should be based upon appropriate toxicological data, or limits described in national compendial requirements. Manufacturing processes should be adequately controlled so that the impurities do not exceed such established specifications.

Many excipients are extracted from or purified by the use of organic solvents. These solvents are normally removed by drying the moist excipient. In view of the varying and sometimes unknown toxicity of solvents, it is important that excipient specifications include tests and limits for residues of solvents and other reactants.

Container specifications should be established for all excipients to assure consistency in protecting the product during transport from the excipient manufacturer to the pharmaceutical producer. The specifications should not only provide for containers that maintain the stability of the product, but should also meet requirements for protection during shipping, against insect infestation, during handling, etc.

## 6.3 Batch production records

Computer systems are increasingly used to initiate, monitor, adjust and otherwise control manufacturing processes. These operations may be accompanied by recording charts that show key parameters (e.g. temperature) at suitable intervals, or even continuously, throughout the process. In other cases, key measurements (e.g. pH) may be displayed temporarily on a monitor screen, but are not available in hard copy.

Records showing addition of ingredients, actual performance of operations by identifiable individuals, and other information usually seen in conventional records, may be missing. When computers and other sophisticated equipment are

employed, the emphasis must change from conventional, hand-written records to:

- systems and procedures that show that the equipment and software is in fact performing as intended;
- checking and calibration of the equipment at appropriate intervals;
- retention of suitable back-up systems such as copies of the program and files, duplicate tapes or microfilm;
- assurance that changes in the program are made only by authorized personnel and that they are clearly documented and validated.

#### 6.4 Other documents

Shipping and storage requirements should be established to ensure that the product reaches the manufacturer with proper quality attributes. This should be mutually agreed upon between the vendor and the purchaser and established prior to transportation of the product.

Written procedures should be established and followed for maintenance of the equipment. All maintenance activities performed must be recorded; this may be in the form of a log, computer database or other appropriate documentation, as long as the system can identify who was responsible for performing each function.

## 7. Good practices in production and quality control

### 7.1 Change control and process validation

Process changes may lead to changes in inherent product characteristics. Manufacturers should have a formal process change system in place, with written standard operating procedures covering such changes. Management of the change system should be assigned to an independent quality unit having responsibility and authority for final approval of process changes.

Manufacturers of excipients often produce laboratory or pilot batches. Scale-up to commercial production may involve several stages and data should be reviewed to demonstrate the adequacy of the scale-up process. Scale-up may introduce significant problems of consistency between batches. Pilot batches should serve as the basis for establishing in-process and finished product purity specifications.

Typically, manufacturers will generate reports that discuss the development and limitation of the manufacturing process. Summaries of such reports should be reviewed to determine if the plant is capable of producing the excipient. The reports serve as the basis for the validation of the manufacturing and control procedures, as well as the basic documentation to demonstrate that the process works consistently.

A document comprising scale-up data and describing the process reactions, operating parameters, purifications, impurities and key tests needed for process control should be written. A retrospective analysis of historical data (through statistical data and process capability data analysis) as well as the previous documentation will provide a good basis for validation.

## 7.2 Good practices in production

### **7.2.1 Prevention of cross-contamination**

The potential for cross-contamination should be considered in the design of the manufacturing process and facility. The degree to which cross-contamination should be minimized depends on the safety and intended use of the excipient.

The precautions taken to minimize cross-contamination should be appropriate to the conditions of the manufacturing facility and will take account of the range of materials manufactured. When the excipient product is initially recovered, it should be in a clean environment and not exposed to airborne contaminants, such as dust from other excipient or industrial chemicals. Typically, the damp product will be unloaded into clean, covered containers and transported for drying and other manipulations. These subsequent operations should be performed in separate areas or under controlled conditions because once dry, the excipient is more likely to contaminate its environment, including any surrounding products. The primary consideration is that the building and facilities should not contribute to an actual or potential contamination of the excipient.

The air-handling systems at the site of manufacture should be designed to prevent cross-contamination. In dedicated areas processing the same excipient, it is permissible to recycle a portion of the exhaust air back into the same area. The adequacy of such a system of operation for multi-use areas, especially if several products are processed simultaneously, should be carefully analysed. In multi-use areas where several products are completely confined in closed vessels and piping systems, filtration of the supply air (combined fresh make-up air and recycled air) is acceptable if the conditions are consistent with other existing regulations (e.g. environmental, safety).

In those areas where the excipient is in a damp or moistened form, such as filter or centrifuge cake, and may be exposed to room air, filter efficiencies in the supply air system as low as 85% may be adequate. In those areas where one or more of the products is being processed in a dry form, such filtration may not be enough to prevent cross-contamination. In all cases, manufacturers should be able to demonstrate the adequacy of their air-handling systems.

Excipient manufacturers should have a documented programme identifying all insecticides, pesticides, rodenticides and herbicides used at the site of manufacture. Adequate measures should be taken to prevent these agents from contaminating the excipients.

### 7.2.2 *In-process blending/mixing*

Some processes require blending or mixing. Such in-process blending is acceptable provided it is adequately documented in batch production records. Examples include:

- Collection of multiple batches or continuous accumulation of batches with defined endpoint in a single holding tank (with a new batch number).
- Recycling material from one batch for further use in a subsequent batch.
- Repeated crystallizations of the same mother liquor for better yield of crystals.
- Collecting several centrifuge loads in a single drier/blender.

Incidental carry-over is another type of in-process mixing that frequently occurs. Examples include:

- Residue adhering to the wall of a micronizer used for milling the finished excipient.
- Residual layer of damp crystals remaining in a centrifuge bowl after discharge of the bulk of the crystals from a prior batch.
- Incomplete discharge of fluids, crystals or particles from a processing vessel upon transfer of the material to the next step in the process.

These residues are usually acceptable since clean-up between successive batches of the same excipient is not normally required during production. However, in the case of non-dedicated production units, complete cleaning procedures designed to prevent contamination that would alter the quality of the substance must be employed when changing from one excipient to another. Checking the effectiveness of these cleaning procedures may require the use of analytical testing for the substances involved.

In contrast to in-process blending and incidental carry-over discussed above, other blending operations should be directed towards achieving homogeneity of the finished excipient batch. Three areas in the processing of finished batches of an excipient which should be examined carefully and critically are:

- the final blending operation to produce the finished batch;
- the point in the process at which the batch number is assigned;
- the sampling procedure used to obtain the sample that is intended to be representative of the batch.

Blending of excipient batches to salvage adulterated material is not an acceptable practice.

Mother liquors containing recoverable amounts of excipients are frequently reused. Secondary recovery procedures for such excipients are acceptable, if the recovered excipient meets its specifications and if recovery procedures are indicated in batch production records. Secondary recovery procedures for

reactants and intermediates are acceptable provided that the recovered materials meet suitable specifications.

### **7.2.3 Control of microbial contamination**

The manufacture of sterile excipients for use in aseptic/sterile processing presents technical challenges. It is essential that adequately qualified and trained personnel be used to supervise and perform procedures associated with the manufacture of sterile excipients. The environment in which procedures are conducted, and the operators themselves, are significant potential sources of contamination in aseptic operations. Processes should be designed to minimize contact between excipient and the environment and operators. Those aseptic excipient operations which require considerable operator involvement must have adequate controls. Major potential problem areas include aseptic removal of the excipient from centrifuges, manual transfer to drying trays and mills, and the inability to sterilize the drier. Not all equipment currently in use can be sterilized.

The excipient manufacturer must document the cleaning of critical processing equipment such as centrifuges and driers. Any manipulation of sterile excipients after sterilization must be performed as a validated aseptic process. This is particularly important for those excipients which are not further sterilized prior to packaging into final containers. In some instances, the compendial monographs may specify that an excipient which does not meet parenteral grade standards must be labelled as not suitable for use in the preparation of injectable products.

Some manufacturers of non-sterile excipients use heat, gamma radiation and other methods to reduce the microbial burden. These methods are acceptable provided the manufacturer has shown that the product meets microbial requirements and that the process is under control within the manufacturer's specifications. Any procedure should be validated in accordance with recognized international standards to demonstrate that the process will produce the intended result. Post-production treatment of excipients should not be used as a substitute for attention to microbiological control during production.

A protected environment may be necessary to avoid microbial contamination or degradation caused by exposure to heat, air or light. The degree of protection required may vary depending on the stage of the process. Often, direct operator contact is involved in the unloading of centrifuge bags, transfer hoses (particularly those used to transfer powders), drying equipment and pumps, and equipment should be designed to minimize the possibility of contamination. The sanitary design of transfer and processing equipment should be evaluated. Those with moving parts should be assessed for the integrity of seals and other packing materials to avoid product contamination.

Special environments required by some processes must be monitored at all times to ensure product quality (e.g. inert atmosphere, protection from light). If interruptions in the special environment occur, adequate evidence must be

provided that they have not compromised the quality of the excipient. Such environmental concerns become increasingly important after purification of the excipient has been completed.

The environment to which the excipient may be exposed should be similar to that used in the manufacture of the final dosage form. This is especially true in the case of excipients intended for parenteral dosage forms. For example, controlled areas may need to be established along with appropriate air quality classifications. Such areas should be serviced by suitable air-handling systems and there should be adequate environmental monitoring programmes. Any manipulation of sterile excipient after sterilization must be performed as an aseptic process, using Class 100 air<sup>1</sup> and other aseptic controls.

#### **7.2.4 Water systems/water quality**

While drinking-water is used for many excipient processes, purified water is also widely used. Because of the well-known potential for microbial growth in deionizers and ultrafiltration or reverse-osmosis systems used to produce purified water, such systems must be properly validated and checked. Proper control methods include the establishment of water quality specifications and corresponding action levels, remedial action when microbial levels are exceeded, and adequate maintenance procedures such as regeneration and sanitation/sterilization.

Appropriate specifications for chemical and microbial quality should be established and periodic testing conducted. Such specifications will vary depending on the process and the point in the process when the water is used. For example, in some cases, if the water is used in later processing steps such as for a final wash of the filter cake, or if the excipient is crystallized from an aqueous system, the water quality standards may need to be higher than normally specified for purified water. This is particularly important where the excipient's intended use is in parenteral dosage forms. The frequency of microbial and chemical testing of purified water depends on a variety of factors, including the test results and the point in the process (e.g. final wash in centrifuge) at which such water is used.

Most purified water and water for injection systems, including reverse-osmosis and ultrafiltration systems, have the potential for endotoxin contamination. If the final excipient is supposed to be pyrogen free or sterile, or will be used in preparing parenteral products, validation of the system to control endotoxins should be conducted and routine testing of the process water for

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<sup>1</sup> Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992, Annex 1, Section 17.3 (WHO Technical Report Series, No. 823). In this volume, see p. 88.

endotoxins should be performed (preferably by the LAL (*Limulus* amoebocyte lysate) method).

### **7.2.5 Packaging operations**

When the programme for packaging operations is being set up, particular attention should be given to minimizing the risk of cross-contamination, mix-ups, or substitutions. Different products should not be packaged in close proximity unless there is physical segregation or the use of electronic surveillance.

### **7.2.6 Delivery**

The manufacturer should arrange for the protection of the product after final inspection and testing. Where contractually agreed, this protection should include delivery to destination. Distribution records should be kept.

## 7.3 Good practices in quality control

### **7.3.1 General**

The quality control unit, in addition to having the responsibility and authority to approve or reject all components, in-process materials, packaging materials and finished excipients, and to review production records, etc., should also be responsible for approving or rejecting excipients manufactured, processed, packaged, or held under contract by another company, as well as for approving or rejecting all procedures, specifications and process changes having an effect on the quality of the excipient.

### **7.3.2 Control of starting materials**

All starting materials must be tested or otherwise verified prior to use. Verification should include a certificate of analysis from the supplier and, wherever feasible, an identification test. There should be clear guidance or standard operating procedures established for the approval of each starting material.

Starting materials are usually subjected to an identity test and additional testing to confirm that they meet appropriate specifications. Some starting materials may not be acceptance tested by the manufacturer because of the hazards involved or other valid considerations. In such cases, quality certification for each batch from the vendor should be on file. There should always be some evidence of an attempt by the excipient manufacturer to establish identity, even if it is only a visual examination of containers, examination of labels, or recording of batch numbers from the labels.

### **7.3.3 In-process testing**

In-process inspection and testing should be performed by monitoring the process or by actual sample analysis at defined locations and times. The results should conform to established process parameters or acceptable tolerances. Work instructions should delineate the procedure to follow and how to use the inspection and test data to control the process.

### **7.3.4 Quality records and retention samples**

The manufacturer should establish and maintain procedures for identification, collection, indexing, filing, storage, maintenance and availability of quality records. Quality records should be maintained to demonstrate achievement of the required quality and the effective operation of the quality system. These data should include pertinent subcontractor quality records.

All quality records should be legible and identifiable with the product involved. Quality records should be stored and maintained in such a way that they are readily retrievable, in facilities that provide a suitable environment to minimize deterioration or damage and to prevent loss. Retention times of quality records should be established and recorded. Where agreed contractually, quality records should be made available for evaluation by the purchaser or the purchaser's representative for an agreed period.

All appropriate records relating to inspection and testing must be available for review. Where the process is continuously monitored, acknowledgement must be made of this and the results of the monitoring should be available.

Reserve samples of the released excipient should be retained for one year after the expiry or re-evaluation date, or for one year after distribution is complete. Sample size should be twice the amount required to perform release specification testing.

### **7.3.5 Stability studies**

Many excipient products are very stable and may not require extensive testing to check stability. The stability of some excipients may be affected by undetected changes in starting material specifications, or subtle changes in manufacturing procedures. Excipients may also be shipped in a large variety of different packaging types that can affect their stability (e.g. metal and plastic drums, bags, plastic and glass bottles, bulk tankers).

Some excipients may be similar in chemical structure to other excipients, and some may be mixtures or blends of other excipients. These excipients may be very similar to others within a product group. Minor quantitative differences of some of the components may be the only significant variation from one product to another. For these excipients, a "model product" approach to assess the stability may be appropriate. Stability studies of this type should involve selection of several "model products" that would be expected to simulate the stability of the

product group being assessed. This selection must be scientifically based. Data from stability studies of these “model products” can be used to determine the theoretical stability of similar products.

The full stability testing programme, when needed, usually contains the following features and takes into account historical data:

- The programme should be formalized in writing and ongoing studies should be reviewed at least annually.
- The programme should periodically include a sample from at least one commercial size batch.
- Stability samples should be stored in containers that approximate the primary market container. Simulations of all types of containers are not required, unless there are theoretical reasons to indicate that stability may be affected by container type.
- The samples should be stored under conditions similar to those recommended for the marketed excipient product.
- Additional samples may be stored under stress conditions (e.g. elevated temperature, light, humidity or freezing) if such conditions might reasonably be encountered during distribution and storage.
- Stability-indicating test methods should be used.
- Where stability of the excipient appears to be a significant issue in its use in pharmaceutical manufacturing, additional periodic testing of either the specific material or “model products” may have to be performed to ensure that the expected stability does not significantly change with future batches. The frequency of testing should be determined by the impact that the excipient’s stability may have on its usage.

### ***7.3.6 Expiry/re-evaluation dating***

Conducting a stability testing programme does not necessarily mean that expiry dates must be used. Where stability testing indicates a limited shelf-life, the label should declare an expiry date or indicate the need for re-evaluation testing at an appropriate interval to assure quality at time of use.

If the need for special storage conditions exists (e.g. protection from light, heat), such restrictions should be placed on the label.

### ***7.3.7 Calibration of measuring and test equipment***

All measuring and test equipment identified as being part of the quality system should be properly calibrated and maintained. This includes all in-process instruments identified as critical quality instruments, as well as test equipment used in the laboratory. The control programme should include the standardization or calibration of reagents, instruments, apparatus, gauges and recording devices at suitable intervals, in accordance with an established written programme containing specific directions, schedules, limits for accuracy and precision, and provi-

sions for remedial action in the event that accuracy and/or precision limits are not met. Reagents, instruments, apparatus, gauges and recording devices not meeting established specifications should not be used. Computer systems used to verify that the product conforms to specifications must be audited to ensure satisfactory performance in the laboratory.