

Annex 5

Good manufacturing practices: supplementary guidelines for the manufacture of pharmaceutical excipients

1. General considerations	51
2. Glossary	54
3. Self-inspection and quality audits	55
4. Equipment	56
4.1 Use of equipment	56
4.2 Cleaning programme	57
4.2.1 Detailed cleaning procedure	57
4.2.2 Sampling plan	57
4.2.3 Analytical methods/cleaning limits	58
5. Materials	58
5.1 General	58
5.2 Starting materials	58
5.3 Rejected and recovered materials	59
5.4 Returned excipients	59
5.5 Storage practices	60
6. Documentation	60
6.1 General	60
6.2 Specifications	61
6.3 Batch production records	61
6.4 Other documents	62
7. Good practices in production and quality control	62
7.1 Change control and process validation	62
7.2 Good practices in production	63
7.2.1 Prevention of cross-contamination	63
7.2.2 In-process blending/mixing	64
7.2.3 Control of microbial contamination	65
7.2.4 Water systems/water quality	67
7.2.5 Packaging operations	67
7.2.6 Delivery	68
7.3 Good practices in quality control	68
7.3.1 General	68
7.3.2 Control of starting materials	68
7.3.3 In-process testing	68
7.3.4 Quality records and retention samples	69
7.3.5 Stability studies	69
7.3.6 Expiry/re-evaluation dating	70
7.3.7 Calibration of measuring and test equipment	71

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.¹ 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 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

¹ 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 (WHO Technical Report Series, No. 823).

(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 conformance 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 measures 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 file¹

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.

pharmaceutical excipients

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

¹ This term appears to be specific to United States regulations.

- 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, 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 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 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 data base 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*

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 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 manipula-

tion 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 manipula-

tion of sterile excipient after sterilization must be performed as an aseptic process, using Class 100 air¹ 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 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

¹ 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).

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 pro-

cedure 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 to 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 provisions 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.