pharmacokinetic comparisons of the chosen route versus transdermal.

Photocarcinogenicity studies may be required and should be considered if data and the proposed use indicate when evaluating materials to be placed on the skin for prolonged periods of time and exposure to UV light is a factor (e.g., sun block). This also applies to oral, parenteral, and inhalation products where skin drug concentrations exceed plasma drug concentrations for a substantial period of time, or where the candidate material would appear to have the potential for photo-activity or has demonstrated photo-activity.

FOR INJECTABLE DOSAGE FORMS:

Background Information—

1. Define compatibility of the dosage form with blood, if appropriate, based on route of exposure.
2. Define the pH and tonicity of injectable dose form, if appropriate, based on the route of exposure.

Baseline Toxicity Data—

- *Effects of Acute Exposure by Intended Injectable Dose Routes*
    1. Include evaluation of injection site irritation in rabbit or dog
    2. Include evaluation of rate of administration.

FOR INHALATION OR INTRANASAL EXPOSURE:[1]

Baseline Toxicity Data—

- *Acute Inhalation Toxicity*—A limit test that would, for example, use the highest achievable concentration in a 4-hour exposure to vapor, aerosol, or solid particulate. Pulmonary sensitization may be performed along with other appropriate studies. If exposure is to be to an aerosol or solid particulate, particulates of appropriate mass median diameter should be generated.
- *Single and Repeated Dose ADME/PK by Inhalation or Intranasal and Oral Routes*
- *28-Day Repeated Dose Inhalation Study in Two Mammalian Species Using Vapor or Particulates of Appropriate Mass Median Diameter:* compare to similar oral toxicity data.

FOR OPHTHALMIC EXPOSURE:

Background Information: define pH and osmolarity of topical ocular dose form.

Baseline Toxicity Data—

- *Effects of Acute Exposure by Ophthalmic Routes:* cytotoxicity tests (e.g., agar overlay)
- *Effects of Repeated Exposures by Ophthalmic Routes*
    1. Studies in two species (one rodent, one mammalian nonrodent)
    2. Examination of anterior and posterior segments of the eye
    3. Studies on allergenicity potential.

Other Data—Comparison of pharmacokinetic parameters of the route chosen for reproductive studies and the ophthalmic exposure are essential for extrapolation of potential toxicity via the ophthalmic route.

DEFINITION OF TERMS

Acute: exposure to a test agent within a single, 24-hour period. Doses may be single, multiple or continuous during a 24-hour period.

Subacute: repeated dosing of a test agent for up to 29 days. Daily doses may be single, multiple or continuous during a 24-hour period.

Subchronic: repeated dosing of a test agent for 30 days to 10% of the lifespan of the test species (90 days in rodents). Daily doses may be single, multiple or continuous during a 24-hour period.

Chronic: repeated dosing of a test agent for more than 10% of the lifespan of the test species (more than 90 days in rodents). Daily doses may be single, multiple or continuous during a 24-hour period.

[1] When designing studies to evaluate use in products intended for use by the inhalation or intranasal route, consideration should be given to the dosing regimen that will be used by humans. The appropriate study protocol for a product intended for inhalation therapy that will result in prolonged exposures (e.g., several hours per day) may differ from that used to evaluate a product that would result in exposure to several metered doses per day.

⟨1078⟩ GOOD MANUFACTURING PRACTICES FOR BULK PHARMACEUTICAL EXCIPIENTS

BACKGROUND

This general information chapter provides guidelines for methods, facilities, and manufacturing controls to be used in the production of pharmaceutical excipients in order to ensure that excipients possess the quality, purity, safety, and suitability for use that they purport to possess. The principles and information in this chapter can be applied to the manufacture of all pharmaceutical excipients (referred to throughout this document as *excipient[s]*) intended for use in human drugs, veterinary drugs, and biologics. It covers the quality management system and the extent of good manufacturing practices (GMP) necessary throughout manufacturing for both batch and continuous processes. It is intended to assist manufacturers as well as auditors in establishing whether the facilities and controls used for the manufacture of excipients are adequate and whether the excipients possess the quality and purity that they purport to possess and are suitable for their intended use. The manufacture of certain excipients for specialist applications presents additional challenges that are outside the scope of this chapter. Examples include excipients for parenteral, ocular, inhalation, and open wound use and those that are sterile and/or pyrogen-free. It does not provide information for all national legal requirements nor does it cover in detail the particular characteristics of every excipient. The quality system standard used as a framework for this chapter is ISO 9001, which is appropriate to manufacturing. Because of the diversity of excipients, some principles in this information chapter may not be applicable to certain products and processes.

This chapter combines the concepts of existing GMP principles from the following sources:

- World Health Organization (WHO) GMP Guidelines for Excipients,
- International Pharmaceutical Excipients Council (IPEC) Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients 2001,
- Institute of Quality Assurance (IQA) Pharmaceutical Quality Group (PQG) PS 9100:2002, Pharmaceutical Excipients,
- International quality management system requirements as developed by the International Organization for Standardization (ISO).

In view of the increasing globalization of the pharmaceutical industry and the harmonization of pharmaceutical registration requirements, deference to all schemes is becoming necessary. Therefore, relevant portions of the manufacturing concepts are employed throughout this chapter.

The *General Guidance* section provides an overview of the appropriate manufacturing practice criteria applicable to excipient manufacture and the points of application of excipient good manufacturing practices and quality systems. The

section also recommends measures to limit contamination of an excipient. Finally, it discusses the relationship of excipients to finished dosage forms. No attempt has been made to include details specific to particular excipients.

The information in *Appendix 1. Auditing Considerations* sets forth key criteria to aid in the audit of an excipient manufacturing facility.

For a list of terms used in this chapter and their definitions, see *Appendix 2. Glossary.*

INTRODUCTION

Purpose and Scope

This chapter defines the extent and point of application of appropriate GMP principles for excipient manufacture and is applicable to the manufacture of excipients intended for use in drug products. It covers the quality management system and the extent of GMP necessary throughout manufacturing for both batch and continuous processes. It is intended to aid both auditors and manufacturers in establishing whether the facilities and controls used for the manufacture of excipients are adequate and whether the excipients possess the quality, purity, and safety that they purport to possess and are suitable for their intended use.

The manufacture of certain excipients for specialist applications presents additional challenges that are outside the scope of this chapter. Examples include excipients

- for parenteral, ocular, inhalation, and open wound use; and
- those that are purported to be sterile and/or pyrogen-free.

In these cases, detailed information pertaining to the intended use of an excipient as provided by the end user can be useful in determining appropriate GMP. This chapter does not address the specific GMP relating to good trade and distribution practices (GTDP).

Principles Adopted

The Chapter and Its Use—Pharmaceutical excipients are diverse and often have uses other than pharmaceutical applications. Each manufacturer should consider how the chapter might apply to its products and processes (for example, batch versus continuous processes). Because excipients are so diverse, some principles of this chapter may not be applicable to certain products and manufacturing processes.

Application—The text provides information necessary for the manufacture of excipients but does not provide all the details. It cannot specify national legal requirements or cover particular characteristics of every excipient.

Quality System Standard—The quality management system standard chosen as a framework for this chapter is ISO 9001, which is appropriate for manufacturing facilities. A manufacturer may apply the ISO standard with or without certification; but this possibility, as a business decision, is not discussed in this chapter. However, ISO certification has the benefit of providing assurance to customers that the excipient manufacturers quality management system has been independently verified.

The headings in this chapter have been aligned with the ISO 9001 clause numbers, because many excipient manufacturers already use that standard as a basis for their quality management system. Additional headings are included as needed to introduce additional guidance on GMP when not covered by current ISO 9001 clauses.

Document Structure—The chapter combines the concepts of existing GMP principles from the following:

- World Health Organization (WHO), GMP Guidelines for Excipients,
- International Pharmaceutical Excipients Council (IPEC), Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients 2001,
- Institute of Quality Assurance (IQA) Pharmaceutical Quality Group (PQG) PS 9100:2002, Pharmaceutical Excipients,
- International quality management system requirements as developed by the International Organization for Standardization (ISO).

In view of the increasing globalization of the pharmaceutical industry and the harmonization of pharmaceutical registration requirements, relevant portions of the manufacturing concepts detailed in these schemes are employed throughout this chapter.

The *General Guidance* section provides an overview of the GMP criteria applicable to excipient manufacture and the point of application of excipient GMP.

The remaining sections provide guidance on GMP principles and implementation of a quality management system suitable for excipient manufacture. For example, these sections suggest measures to limit excipient contamination. No attempt has been made to include details specific to particular excipients, and individual manufacturers should address these as they apply to their own products and processes.

The Appendixes provide supporting guidance for excipient GMP. *Appendix 1. Auditing Considerations* describes key criteria to be considered in the audit of an excipient manufacturing facility. *Appendix 2. Glossary* provides definitions of terms used in this chapter.

GENERAL GUIDANCE

Pharmaceutical Excipients—Pharmaceutical excipients are substances other than the active pharmaceutical ingredient (API) that have been appropriately evaluated for safety and are intentionally included in a drug delivery system. For example, excipients can do the following:

- 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, and
- enhance any other attribute of the overall safety, effectiveness, or delivery of the drug during storage or use.

A more complete classification of excipients according to their functions can be found in *USP and NF Excipients, Listed by Category* in the *USP–NF.*

Excipient GMP Implementation—The application of GMP is relevant once it has been determined that a chemical is intended for use as a component of a drug product. Excipient manufacture should be carried out in accordance with the GMP concepts consistent with this chapter. The objective of excipient GMP is to ensure that the manufacture of an excipient results in a consistent material with the desired quality characteristics. The emphasis of GMP for excipients is to ensure product integrity, avoid product contamination, and ensure that records are maintained.

As the excipient manufacturing process progresses, the degree of assurance concerning the quality of the product should increase. Manufacturing processes should be controlled and documented. However, at some logical processing step, as determined by the manufacturer, the GMP as described in this chapter should be applied and maintained.

Judgment based on risk analysis and a thorough knowledge of the process is required in order to determine from which processing step GMP should be implemented. This is usually well before the final finishing operation and, for example, may be identified using methods such as hazard analysis and critical control point (HACCP), failure mode and effects analysis (FMEA), or a detailed process flow diagram.

Consideration should also be given to other factors such as batch versus continuous processing, dedicated versus multipurpose equipment, and open versus closed processes.

QUALITY MANAGEMENT SYSTEM: EXCIPIENT QUALITY SYSTEMS

General Recommendations

The principles outlined in this chapter provide a comprehensive basis for the quality management system used in the manufacture of pharmaceutical excipients. Excipient manufacturers should identify the quality management processes required to ensure excipient quality. Where manufacturing, testing, or other operations that could affect excipient quality are outsourced, the responsibility for quality remains with the excipient manufacturer, and control measures should be defined (see also the subsection *Purchasing Information* in the *Product Realization* section).

Documentation Recommendations

General—The excipient manufacturer should have a system in place to control documents and data that relate to the requirements of the quality management system.

Quality Manual—The excipient manufacturer should prepare a quality manual describing the quality management system, the quality policy, and the commitment of the excipient manufacturer to applying the appropriate GMP and quality management standards contained in this chapter. This manual should include the scope of the quality management system, reference to supporting procedures, and a description of the interaction between quality management processes.

Control of Documents—The excipient manufacturer should establish and maintain procedures for the identification, collection, indexing, filing, storage, maintenance, and disposition of controlled documents, including documents of external origin that are part of the quality management system.

Procedures used in the manufacture of excipients should be documented, implemented, and maintained. In addition, there should be formal controls relating to procedure approval, revision, and distribution. These controls should provide assurance that the current version of a procedure is being used throughout the operational areas and that previous revisions of documents have been removed.

Documents and subsequent changes to documents should be reviewed and approved by designated qualified personnel before issuance to the appropriate areas, as identified in the documents. Documents that affect product quality should be reviewed and approved by the quality unit (see also *Responsibility and Authority* in the section *Responsibility, Authority, and Communication* under *Management Responsibility*).

Controlled documents may include a unique identifier, the date of issue, and a revision number to facilitate identification of the most recent document. The department with the responsibility for issuing the documents should be identified. When it is practical, changes and the reasons for the changes should be documented.

Electronic documentation should meet the requirements for the document control system stated above. If electronic signatures are used on documents, they should be controlled to provide security equivalent to that provided by a handwritten signature. Electronic documents and signatures may also have to satisfy local regulatory requirements.

Control of Records—The excipient manufacturer should establish and maintain procedures for the identification, collection, indexing, filing, storage, maintenance, and disposition of records.

Records should be maintained to demonstrate achievement of the required quality and the effective operation of the quality management system. Records should be legible and identifiable with the product involved. Pertinent subcontractor quality data should be an element of these records.

Entries in records should be clear, indelible, made directly after performing the activity (in the order performed), and signed and dated by the person making the entry. Corrections to entries should be signed and dated, leaving the original entry legible.

Records should be kept for a defined period. This period should be appropriate to the excipient and to its expiry date or reevaluation interval. Records should be stored and maintained in such a manner that they are readily retrievable, in facilities that provide an environment suitable for minimizing deterioration or damage.

Change Control—The excipient manufacturer should establish and maintain procedures to evaluate and approve changes that may affect the quality of the excipient. For example, this may include changes to the following:

- raw materials or packaging and their sources,
- material specifications,
- test methods,
- manufacturing and analytical equipment,
- production processes,
- manufacturing or packaging sites.

A unit with a function that is independent from production (such as regulatory affairs or quality assurance) should have the responsibility and authority for the final approval of changes.

Customers should be notified, and, where applicable, excipient regulatory submissions (for example, for Drug Master Files [DMFs] or Certificates of Suitability to the *European Pharmacopoeia* [CEPs]) should be amended to reflect significant changes from established production and process control procedures that may affect excipient quality (see also *Customer Communication* in the section *Customer-Related Processes* under *Product Realization*).

MANAGEMENT RESPONSIBILITY

Management Commitment

Top management should demonstrate to the organization the importance it places on customer satisfaction and compliance with the appropriate regulations and standards. This should be accomplished through the development of a quality policy and establishment of quality objectives. Progress toward the documented quality objectives should be reviewed at planned intervals.

Customer Focus

It is the responsibility of top management to ensure that customer requirements are determined and met. The excipient manufacturer should permit the customer or its representative to conduct audits of the manufacturers quality management system, manufacturing processes, buildings, and facilities.

Quality Policy

Top management should demonstrate its commitment to the corporate quality policy and ensure that it is implemented within the operational unit. The quality policy should support continual improvement of the quality management system. Management should participate in the de-

velopment of the companys quality policy and provide the resources necessary for its development, maintenance, and deployment.

Planning

Quality Objectives—Top management should set objectives for adherence to GMP to ensure that the excipient manufacturer maintains and improves its performance. Objectives should be deployed throughout the organization and should be measurable and consistent with the quality policy.

Quality Management System Planning—Top management should provide adequate resources to ensure conformity to the provisions of this chapter. There should be a process for the identification of resources needed for adherence to GMP. A gap analysis based on audits by internal personnel, customers, regulatory agencies, or outside contractors, or based on the use of this chapter, could be created to identify resource requirements. Top management should ensure that the integrity of the quality management system is maintained when changes are planned and implemented.

Responsibility, Authority, and Communication

Responsibility and Authority—Responsibility and authority should be clearly defined by top management and communicated within the organization. It should be the responsibility of a unit that is independent of production, such as the quality unit, to do the following:

- ensure that quality-critical activities are undertaken as defined,
- approve suppliers of quality-critical materials and services,
- approve or reject raw materials, packaging components, intermediates, and finished excipients,
- ensure that there is a review of production records to confirm that no errors have occurred or, if errors have occurred, that they are fully investigated,
- participate in reviewing and authorizing changes to processes, specifications, procedures, and test methods that potentially affect quality (also see above, *Change Control* in the section *Documentation Recommendations* under *Quality Management System: Excipient Quality Systems*) and participate also in investigating failures and complaints,
- retain responsibility for approval or rejection of the excipient if it is produced, processed, packaged, or held under contract by another company,
- develop and implement a self-inspection program of the quality management system.

The excipient manufacturer may delegate some of the quality units activities to other personnel if appropriate controls (for example, periodic audits, training, and documentation) are in place.

An organization chart by function should show interdepartmental relationships as well as relationships to top management of the company. Personnel whose positions affect excipient quality should have job descriptions.

Management Representative—The excipient manufacturer should appoint a management representative with sufficient authority to ensure that the provisions of this chapter are properly implemented. The representative should periodically report to top management on conformity to the quality management system, including changing customer and regulatory requirements.

Internal Communication—The excipient manufacturer should ensure that appropriate systems are established to communicate GMP and regulatory requirements, quality policies, quality objectives, and procedures throughout the organization. The communication should also provide information about the effectiveness of the quality management system. Top management should be notified promptly of quality-critical situations, such as product retrievals, in accordance with a documented procedure.

Management Review

General—The top management of the company should hold periodic reviews of the quality management system to confirm the organizations continued conformity to this chapter. The review should be recorded and should include assessing opportunities for improvement and the need for changes to the quality management system.

Review Input—Management review inputs should include, for example, the following:

- results of internal and external audits,
- customer feedback of the company performance,
- product conformity and process performance,
- action items from the previous management review,
- customer complaints,
- status of corrective or preventive actions,
- changes that could affect the quality management system.

Review Output—The management review should identify the resources needed and the opportunities presented for improving the quality management system and improving product conformity to customer and regulatory requirements. A record should be made of actions recommended and taken.

RESOURCE MANAGEMENT

Provision of Resources—There should be sufficient qualified personnel and resources (e.g., equipment, materials, buildings, and facilities) to implement, maintain, and improve the quality management system and to produce, package, test, store, and release each excipient in a manner consistent with this chapter.

Human Resources

General—Personnel performing work affecting the quality of excipients should have the appropriate combination of education, training, and experience for their assigned tasks. Consultants advising on the design, production, packaging, testing, or storage of excipients should have sufficient education, training, and experience or any combination thereof to advise on the subject for which they are retained. Records should be maintained listing the name, address, and qualifications of consultants and the type of service they provide.

Competence, Awareness, and Training—The excipient manufacturer should establish and maintain procedures for identifying training needs and for providing the necessary training to personnel performing activities affecting excipient quality. Appropriate records of training should be maintained. Training should address the particular operations that the employee performs and GMP as they relate to the employees functions. Qualified individuals should conduct GMP training frequently enough to ensure that employees remain familiar with applicable GMP principles. Management should establish adequate and continued personal-hygiene training for personnel who handle materials so that they understand the precautions necessary for preventing contamination of excipients. The training program should ensure that personnel understand that deviations from procedures may affect the customers product quality.

Personnel Hygiene—To protect excipients from contamination, protective apparel such as head, face, hand, and arm coverings should be worn as appropriate to the duties performed. Jewelry and other loose items, including those in pockets, should be removed or covered. Only authorized

personnel should enter the areas of the buildings and facilities designated as limited-access areas.

Personnel should practice good sanitation and health habits. Any person shown by either medical examination or supervisory observation to have an apparent illness or open lesions that may adversely affect the safety or quality of the excipient should be excluded from direct contact with raw materials, packaging components, intermediates, and finished excipients until the condition is corrected or until competent personnel determine that it will not jeopardize the safety or quality of the excipient. Personnel should be instructed to report to supervisory personnel any health conditions that may have an adverse effect on excipients. The storage and use of food, drink, personal medication, tobacco products, or similar items should be restricted to designated locations separate from manufacturing areas.

Infrastructure—The infrastructure should be managed, operated, cleaned, and maintained in accordance with GMP principles to ensure excipient quality and to avoid contamination (including, where critical to excipient quality, control of particulate matter, microbiological control, and control of water quality).

Buildings and Facilities—The prevention of contamination should be considered in the design of the manufacturing processes and facilities, particularly when the excipient is exposed. Buildings and facilities used in the production, processing, packaging, testing, or storage of an excipient should be maintained in a good state of repair and should be of suitable size, construction, and location to facilitate cleaning, maintenance, and correct operation appropriate to the type of processing.

Manufacturing processes associated with the production of highly sensitizing or toxic products (for example, herbicides and pesticides) should be located in dedicated facilities or should use equipment separate from that used for excipient manufacture. If this is not possible, appropriate measures (for example, cleaning, inactivation) should be implemented to avoid cross-contamination. The effectiveness of these measures should be demonstrated. There should be adequate facilities for the testing of raw materials, packaging components, intermediates, and finished excipients.

Equipment—Equipment used in the production, processing, packaging, testing, or storage of an excipient should be maintained in a good state of repair and should be of suitable size, construction, and location to facilitate cleaning, maintenance, and correct operation, depending on the type of processing (for example, batch versus continuous). Equipment should be commissioned before use to ensure that it is functioning as intended. Where equipment is located outdoors, there should be suitable controls to minimize the risk to excipient quality from the environment (for example, processing within a closed system).

Equipment Construction—Process equipment should be constructed so that contact surfaces will not be reactive, additive, or absorptive and thus will not alter the quality of the excipient. Substances required for operation, such as lubricants or coolants, should preferably not come into contact with raw materials, packaging materials, intermediates, or finished excipients. Where contact is possible, substances suitable for use in food applications should be employed.

Equipment should be designed to minimize the possibility of contamination caused by direct operator contact in activities such as the unloading of centrifuge bags, the use of transfer hoses (particularly those used to transfer powders), and the operation of drying equipment and pumps. The sanitary design of transfer and processing equipment should be evaluated. To control the risk of contamination, equipment with moving parts should be assessed with regard to the integrity of seals and packing materials.

Equipment Maintenance—Documented procedures should be established and followed for maintenance of critical equipment used in the production, processing, packaging, testing, or holding of the excipient. There should be records of the use and maintenance of quality-critical equipment. These records can be in the form of a log, computer database, or other appropriate documentation.

Computer Systems—Computer systems that may affect excipient quality should have sufficient controls for operation and maintenance and for prevention of unauthorized access or changes to computer software, hardware, or data, including the following:

- systems and procedures that show that the equipment and software are performing as intended,
- procedures for checking the equipment at appropriate intervals,
- retention of suitable back-up or archival systems such as copies of the program and files,
- assurance that changes are verified and documented and are made only by authorized personnel.

Utilities—Utilities (for example, nitrogen, compressed air, and steam) used in the production, storage, or transfer of materials that could affect excipient quality should be assessed and appropriate action taken to control the risk of contamination and cross-contamination.

Water—Water used in the manufacture of excipients should be demonstrated to be of appropriate quality in consideration of purity requirements and the intended use of the excipient. Unless otherwise justified, process water should, at a minimum, meet regulatory requirements for drinking (potable) water. If drinking (potable) water is insufficient to ensure quality, or if tighter chemical and/or microbiological water quality specifications are required, appropriate controls and specifications should be set: for example, physical and chemical attributes, total microbial counts, and limits on objectionable organisms and/or endotoxins.

Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process should be specified and monitored with appropriate action limits. Water that comes into contact with the excipient should be supplied under continuous positive pressure (or other means of preventing back flow) in a system free of defects to control the risk of contamination to the excipient.

Work Environment—Where the excipient is exposed during manufacture, it should be in an environment appropriate for minimizing contamination. The manufacturer should apply suitable controls to maintain that environment.

Air Handling—Where an air-handling system is installed to provide protection to the excipient, the excipient manufacturer should demonstrate its effectiveness. Excipient production unit air-handling systems should be designed to prevent cross-contamination. For 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 for multiuse areas, especially if several products are processed simultaneously, should be assessed for potential cross-contamination.

Controlled Environment—A controlled environment may be necessary in order to avoid 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. Special environments required by some processes should be monitored to ensure product quality (for example, inert atmosphere or protection from light). Where an inert atmosphere is required, the gas should be treated as a raw material. If interruptions in the special environment occur, adequate evidence and an appropriate rationale should be documented to show that such interruptions have not compromised the quality of the excipient. Such environmental concerns become increasingly important following purification of the excipient.

Cleaning and Sanitary Conditions—Adequate cleanliness is an important consideration in the design of excipient manufacturing facilities. Buildings used in the production, processing, packaging, or holding of an excipient should be maintained in an appropriately clean and sanitary condition according to the type of processing conducted (for example, open/closed systems). Where maintenance of clean and

sanitary conditions is critical to excipient quality, documented procedures should assign responsibility for cleaning and sanitation, describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities. These procedures should be followed, and cleaning should be documented. Waste should be segregated and disposed of in a timely and appropriate manner. If waste is not disposed of immediately, it should be suitably identified.

Pest Control—Buildings should be free from infestation by rodents, birds, insects, and other vermin. Some raw materials, particularly botanicals, may contain some unavoidable contamination, such as rodent or other animal filth or infestation. The manufacturer should have sufficient control methods to prevent the increase of such contamination or infestation in holding areas and its spread to other areas of the plant.

Lighting—Adequate lighting should be provided to facilitate cleaning, maintenance, and proper operations.

Drainage—In areas where the excipient is open to the environment, drains should be of adequate size and, where connected directly to a sewer, should be provided with an air break or other mechanical device to prevent back-siphoning.

Washing and Toilet Facilities—Adequate personal washing facilities should be provided, including hot and cold water, soap or detergent, air dryers or single-service towels, and clean toilet facilities easily accessible to working areas. Adequate facilities for showering and/or changing clothes should be provided, where appropriate.

PRODUCT REALIZATION

Planning of Product Realization—The excipient manufacturer should plan and develop the processes and controls needed for product manufacture. These plans and controls should be appropriate to the production process, excipient specification, equipment, and facilities used in the manufacture of the product. Key aspects of the planning of a suitable process and its controls should include the following, as appropriate:

- documented testing programs, for quality-critical materials including excipients, that include appropriate specifications, sampling plans, and test and release procedures,
- generation and maintenance of records (also see above, *Control of Records* in the section *Documentation Recommendations* under *Quality Management System: Excipient Quality Systems*) that provide evidence that these plans have been realized as intended and that enable traceability to be demonstrated (also see below in this section, *Traceability* under *Identification and Traceability*),
- provision of resources to implement these plans,
- environmental and hygiene control programs to minimize contamination.

Customer-Related Processes

Determination of Requirements Related to the Product—The excipient manufacturer should determine the excipient quality, labeling, and delivery requirements of the customer. Additional requirements, whether customer-specific, legal, or regulatory (for example, pharmacopeia material and general monographs), should be agreed on by both parties. Requirements not stated by the customer but necessary for specified or intended use, where known, should be considered.

Review of Requirements Related to the Product—The excipient manufacturer and customer should mutually agree upon the requirements identified in the section above, *Determination of Requirements Related to the Product*, before supply commences. The manufacturer should have the facility and process capability to consistently meet the mutually agreed-upon specifications. Where the requirements determined in the section *Determination of Requirements Related to the Product* are changed, this review should be repeated before supply recommences.

Customer Communication—There should be provision for providing accurate and pertinent communication to the customer. Master copies of documents such as specifications and technical reports should be controlled documents. Provision should be made for replying to customer inquiries, contracts, and order-handling requirements. Customer feedback and complaints should be documented. Customers should be notified of significant changes (also see above, *Change Control* in the section *Documentation Recommendations* under *Quality Management System: Excipient Quality Systems*).

Design and Development—ISO 9001 includes requirements for ensuring control over design and development activities. It is recommended that companies involved in such activities follow the requirements of ISO 9001. Full GMP are not always applicable during the design and development of new excipients and/or manufacturing processes. However, development batches of excipients that are intended for use in drug products should be manufactured in accordance with the applicable provisions of this chapter.

Purchasing

Purchasing Process—Excipient manufacturers should have a system for selecting and approving suppliers of quality-critical materials and services (for example, subcontract manufacturers and laboratories). Supplier approval by the quality unit should require an evaluation of the suppliers quality management system, including adequate evidence that they can consistently meet agreed-upon specifications and maintain traceability. This may require periodic audits of the suppliers manufacturing facility. Records of these activities should be maintained. Materials should be purchased against an agreed specification from approved suppliers.

Purchasing Information—Purchasing agreements should describe the material or service ordered, including, where critical to excipient quality, the following:

- the name, type, class, style, grade, item code number or other precise identification traceable to the raw material and packaging specifications,
- drawings, process requirements, inspection instructions and other relevant technical data, including requirements for approval or qualification of product, procedures, process equipment, and personnel,
- adherence to the appropriate sections of this chapter for relevant contract manufacturers or laboratories, and
- a statement to notify the excipient manufacturer of significant changes in quality-critical raw materials.

Verification of Purchased Product—There should be procedures for the approval and release of quality-critical material. Upon receipt, quality-critical materials should be placed in quarantine and should not be used prior to acceptance. Effective quarantine can be established with suitable identifying labels, signs, and/or other manual documentation systems. When quarantine and stock control are managed with computer systems in lieu of a physical stock control, system controls should prevent the use of unreleased material. Quarantine may not be feasible for materials supplied via pipelines. In these cases the excipient manufacturer should establish an agreement with the supplier so that the manufacturer is notified of material that does not meet specification. Sampling activities should be conducted under defined conditions, in accordance with a defined sampling method and using procedures designed to prevent contamination and cross-contamination.

Quality-critical materials used in the manufacture of an excipient should be tested or otherwise verified prior to use. Verification should include availability and a check of the

supplier certificate of analysis and, wherever feasible, at least an identification test. Testing schedules should be organized to separate routine tests from those that are performed infrequently or only for new suppliers. Bulk deliveries should have additional controls to ensure material purity and freedom from contamination (for example, dedicated tankers, tamper-evident seals, a certificate of cleaning, analytical testing, or audit of the supplier). These procedures, activities, and results should be documented.

Production and Service Provision

Control of Production and Service Provision—Production activities should be carried out under controlled conditions (also see above, *Planning of Product Realization* under *Product Realization*). Specific examples of important controls, some of which may not be applicable to all excipient manufacturers, are illustrated in the following sections.

Production Instructions and Records—Production instructions and records are required but may differ for the type of operation: for example, batch versus continuous processes. There should be a controlled document that describes how the excipient is produced (for example, master production instructions, master production and control records, or process definitions). For batch processes, an accurate reproduction of the appropriate master production instructions should be issued to the production area. For continuous processes, a current processing log should be available. Records should be available for each batch of excipient produced and should include complete information relating to the production and control of each batch. For continuous processes, the batch and its records should be defined (for example, based on time or defined quantity). Records may be in different locations but should be readily retrievable. Records for both batch and continuous processing, where critical to excipient quality, should include the following:

- date and time each step was completed or date and time log of key parameters,
- identification of persons performing and directly supervising or checking each significant step, operation or control parameter,
- identification of major equipment and lines used,
- material inputs to enable traceability: for example, batch number and quantities of raw material/intermediate and time it was added,
- in-process and laboratory control results,
- the quantity produced for the defined batch and a statement of the percentage of theoretical yield, unless not quantifiable (for example, as in some continuous processes),
- inspection of the packaging and labeling area before and after use,
- labeling control records,
- description of excipient product containers and closures,
- description of sampling performed,
- failures, deviations and their investigations,
- results of final product inspection.

Equipment Cleaning—The manufacturer should design and justify cleaning and sanitization procedures and provide evidence of their effectiveness. In multipurpose plants the use of the *model product* approach (groups of product of similar type) may be used in justifying a suitable procedure. Cleaning and sanitization procedures should be documented. They should contain sufficient detail to allow operators to clean each type of equipment in a reproducible and effective manner. There should be a record confirming that these procedures have been followed. Equipment and utensils should be cleaned and sanitized where critical to excipient quality and at appropriate intervals to prevent contamination and cross-contamination of the excipient. The cleaning status of equipment should be recorded appropriately.

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 (also see below in this section, *Records of Equipment Use*). During a production campaign, incidental carryover frequently occurs, and it is usually acceptable because cleanup between successive batches of the same excipient is not normally required in order to maintain quality levels. Products that leave residues that cannot be effectively removed should be produced in dedicated equipment. For continuous processing, the frequency of equipment cleaning should be determined by the manufacturer and justified.

Recovery of Solvents, Mother Liquors, and Second Crop Crystallizations—Where solvents are recovered and reused in the same process or different processes, they should meet appropriate standards prior to reuse or mixing with other approved material. Mother liquors or filtrates containing recoverable amounts of excipient, reactants, or intermediates are frequently reused. Such processes should be documented in the production records or logs to enable traceability.

In-Process Blending or Mixing—In-process blending or mixing to ensure batch uniformity or to facilitate processing should be controlled and documented. If the intent of the operation is to ensure batch uniformity, it should be performed so as to ensure homogeneous mixing of materials to the extent feasible and should be reproducible from batch to batch.

In-Process Control—In-process inspection and testing, based on monitoring the process or actual sample analysis at defined locations and times, should be performed. Sampling methods should be documented to ensure that the sample is representative and clearly labeled. In-process samples should not be returned to production for incorporation into the final batch.

The results of in-process tests should be recorded and should conform to established process parameters or acceptable tolerances. Work instructions should define the procedure to follow and should indicate how to use the inspection and test data to control the process. There should be defined actions to be taken when the results are outside specified limits. Where approval to continue with the process is issued within the production department, the specified tests should be performed by trained personnel and the results recorded.

Packaging and Labeling—Procedures should be employed to protect the quality and purity of the excipient when it is packaged and to ensure that the correct label is applied to all containers. Packaging and labeling operations should be designed to prevent mix-ups. Procedures should be implemented to ensure that the correct labels are printed and issued and that the labels contain the correct information. The procedure should also specify that excess labels are immediately destroyed or returned to controlled storage. Excess labels bearing batch numbers should be destroyed. Packaging and labeling facilities should be inspected immediately before use to ensure that materials that are not required for the next packaging operation have been removed. When excipients are labeled on the packaging line, packaged in preprinted bags, or bulk-shipped in tank cars, there should be documentation of the system used to satisfy the intent of the above procedures.

Records of Equipment Use—Records of quality-critical equipment use should be retained. These records should allow the sequence of cleaning, maintenance, and production activities to be determined.

Validation of Processes for Production and Service Provision—An important factor in the assurance of product quality includes the adequate design and control of the manufacturing process, because product testing alone is not sufficient to reveal variations that may have occurred. Each

step of the manufacturing process should be controlled to the extent necessary for ensuring that the excipient meets established specifications. The concept of process validation is a key element in ensuring that these quality assurance goals are met. The process reactions, operating parameters, purification steps, impurities, and key tests needed for process control should be documented, thus providing the basis for validation.

The full validation program that is typically performed in the pharmaceutical industry may not always be carried out by the excipient manufacturer. However, the excipient manufacturer should demonstrate the consistent operation of each manufacturing process: for example, through process capability studies, development, and scale-up reports.

Identification and Traceability

Traceability—Quality-critical items (for example, raw materials, packaging materials, intermediates, and finished excipients) should be clearly identified and traceable through records. These records should allow traceability of the excipient both upstream and downstream. Identification of raw materials used in batch production processes should be traceable through the batch numbering system or other appropriate system. Identification of raw materials used in excipients produced by continuous processing should indicate the time frame during which a particular batch of raw material was processed through the plant. Excipient manufacturers should also have adequate knowledge about the origin of any raw materials derived from plant or animal matter.

Raw materials, including solvents, are sometimes stored in bulk tanks or other large containers, making precise separation of batches difficult. Nevertheless, the use of such materials and containers should be documented in production records.

Inspection and Test Status—There should be a system for identifying the inspection status of quality-critical items, including raw materials, packaging materials, intermediates, and finished excipients. Although storing materials in identified locations is preferred, any means that clearly identifies the test status is satisfactory. Continuously fed materials may need special consideration in order to satisfy these requirements.

Labeling—Labeling for excipient packages is subject to national and international regulatory requirements, which may include transportation and safety measures. At a minimum, labels should include the following:

- the name of the excipient and grade, if applicable,
- the excipient manufacturers and/or distributors name,
- the batch number from which the complete batch history can be determined,
- special storage conditions, if applicable.

Customer Property—The excipient manufacturer should establish and maintain procedures for verification, storage, and maintenance of customer-supplied materials intended for incorporation into the customers excipient. Verification by the manufacturer does not relieve the customer of the responsibility of providing an acceptable material. Material that is lost or that is damaged or otherwise unsuitable for use should be recorded and reported to the customer. In this case, procedures should be in place for acceptable disposition and replacement of the material. The manufacturer should also make provisions for protecting other real and intellectual property that is provided by the customer (for example, test equipment, test methods, and specifications).

Preservation of Product

Handling, Storage, and Preservation—Excipients, intermediates, and raw materials should be handled and stored under appropriate conditions of temperature, humidity, and light so that their identity, quality, and purity are not affected. Outdoor storage of raw materials (for example, acids, other corrosive substances, explosive materials) or excipients is acceptable, provided that the containers give suitable protection against deterioration or contamination of their contents, identifying labels remain legible, and containers are adequately cleaned prior to opening and use. Records of storage conditions should be maintained if they are critical for the continuing conformity of the material to specifications.

Packaging Systems—An excipient packaging system should include the following features:

- documented specifications and examination or testing methods,
- cleaning procedures, where containers are reused,
- tamper-evident seals,
- containers that provide adequate protection against deterioration or contamination of the excipient during transportation and recommended storage,
- containers that do not interact with or contaminate the excipient,
- storage and handling procedures that protect containers and closures and minimize the risk of contamination, damage, or deterioration and that will avoid mix-ups (for example, between containers that have different specifications but are similar in appearance).

If returnable excipient containers are reused, previous labeling should be removed or defaced. If the containers are reused solely for the same excipient, previous batch numbers or the entire label should be removed or completely obliterated.

Delivery and Distribution—Identification and traceability of quality-critical aspects are required of excipient manufacturers. Distribution records of excipient shipments should be kept. These records should identify, by excipient batch, where and to whom the excipient was shipped, the amount shipped, and the date of shipment so as to facilitate retrieval if necessary. Where excipients are handled by a series of different distributors, it should be possible to trace them back to the original manufacturer, and not only to the previous supplier. The manufacturer should maintain the integrity and the quality of the product after final inspection and test. Where contractually specified, this protection should be extended to include delivery to the final destination. Excipients should be supplied only within their expiry and/or retest period.

Control of Measuring and Monitoring Devices—Measuring and test equipment, including computerized systems, identified as being quality-critical should be calibrated and maintained. This includes in-process instruments as well as test equipment used in the laboratory. The control program should include the standardization or calibration of instruments and equipment at suitable intervals in accordance with an established, documented program. This program should contain 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. Calibration standards should be traceable to recognized national or compendial standards as appropriate.

Instruments and equipment not meeting established specifications should not be used, and an investigation should be conducted to determine the validity of the previous results since the last successful calibration. The current calibration status of quality-critical equipment should be known and verifiable to users.

MEASUREMENT, ANALYSIS, AND IMPROVEMENT

The organization should plan and implement the monitoring, measurement, and improvement activities that are required in order to demonstrate conformity of the excipient to customer requirements and to ensure conformity of the

quality management system to this chapter. The organization should evaluate opportunities for improvements through the measurement and analysis of product and process trends.

Monitoring and Measurement

Customer Satisfaction—The excipient manufacturer should establish measurement activities to assess customer satisfaction. Such measurements can include customer complaints, return of excipients, and customer feedback. This information should drive activities that strive to continuously improve customer satisfaction.

Internal Audit—The excipient manufacturer should carry out a comprehensive system of planned and documented internal quality audits. These should determine whether quality activities comply with planned arrangements and should also determine the effectiveness of the quality management system. Audits should be scheduled on the basis of the status and importance of the activity. Audits and follow-up actions should be carried out in accordance with documented procedures. Audit results should be documented and discussed with management personnel having responsibility in the area audited. Management personnel responsible for the area audited should take corrective action on the nonconformities found. *Appendix 1. Auditing Considerations* will be of assistance in establishing an internal audit program.

Monitoring and Measurement of Processes—The excipient manufacturer should identify the tests and measurements necessary for adequately controlling manufacturing and quality management system processes. When critical to excipient quality, techniques used to verify that the processes are under control should be established. When deviations from planned results occur, corrective action should be taken to ensure that the excipient meets requirements. Periodic reviews of key indicators such as process quality attributes and process failures should be conducted to assess the need for improvements.

Monitoring and Measurement of Product—The excipient manufacturer should establish the test methods and procedures to ensure that the product consistently meets specifications. Analytical methods should be suited to their purposes. The analytical methods may be those included in the current edition of the appropriate pharmacopeia or another accepted standard. However, the methods may also be noncompendial. If the excipient manufacturer claims that its product is in compliance with a pharmacopeia or an official compendium, then

- noncompendial analytical tests should be demonstrated to be equivalent to those in the compendia;
- the product should comply with applicable *USP* general chapters and notices.

Laboratory Controls—Laboratory controls should include complete data derived from tests necessary for ensuring conformity with specifications and standards, including the following:

- a description of the sample received for testing, together with the material name, a batch number or other distinctive code, and the date the sample was taken,
- a statement referencing each test method used,
- a record of raw data secured during each test, including graphs, chromatograms, charts, and spectra from laboratory instrumentation, identified to show the specific material and batch tested,
- a record of calculations performed in connection with the test,
- test results and how they compare with established specifications,
- a record of the person who performed each test and the date(s) the tests were performed.

There should be a documented procedure for the preparation of laboratory reagents and solutions. Purchased reagents and solutions should be labeled with the proper name, concentration, and expiry date. Records should be maintained for the preparation of solutions and should include the name of the solution, the date of preparation, and the quantities of material used. Volumetric solutions should be standardized according to an internal method or by using a recognized standard. Records of the standardization should be maintained.

Where used, primary reference reagents and standards should be appropriately stored and need not be tested upon receipt, provided that a certificate of analysis from the supplier is available. Secondary reference standards should be appropriately prepared, identified, tested, approved, and stored. There should be a documented procedure for the qualification of secondary reference standards against primary reference standards. The reevaluation period should be defined for secondary reference standards, and each batch should be periodically requalified in accordance with a documented protocol or procedure.

Finished Excipient Testing and Release—Finished excipient testing should be performed on each batch to ensure that the excipient conforms to documented specifications. There should be a procedure to ensure that appropriate manufacturing documentation, in addition to the test results, is evaluated prior to release of the finished excipient. The quality unit should be responsible for the release of the finished excipient. For excipients produced by continuous processes, assurance that the excipient conforms to documented specifications may be achieved through the results of in-process testing or other process control records.

Out-of-Specification Test Results—Out-of-specification (OOS) test results should be investigated and documented according to a documented procedure. Retest sample results may be used to replace the original test result only if it is demonstrated on the basis of a documented investigation that the original result is erroneous. When statistical analysis is used, both the original and retest data must be included. The OOS procedure should define which statistical techniques are to be used and under what circumstances. These same principles apply when the sample is suspected of not being representative of the material from which it was taken.

Retained Samples—When practical, a representative sample of each batch of the excipient should be retained. The retention period should be appropriate to the expiry or reevaluation date. The retained samples should be stored and maintained in such a manner that they are readily retrievable in facilities that provide a suitable environment. The sample size should be at least twice the amount required to perform complete specification testing.

Certificates of Analysis—The organization should provide certificates of analysis to the required specification for each batch of excipient.

Impurities—When possible, excipient manufacturers should identify and set appropriate limits for impurities. The limits should be based on appropriate safety data, limits as described in official compendia or other requirements, and sound GMP considerations. Manufacturing processes should be adequately controlled so that the impurities do not exceed such established limits. Many excipients are extracted from or purified using organic solvents. These solvents are normally removed by drying. It is important that excipient specifications include tests and limits for solvent residues.

Stability—Although many excipient products are stable and may not require extensive testing to ensure stability, the stability of excipients is an important factor in the overall quality of the drug product. For excipients that have been on the market for a long time, historical data may be used to indicate stability. Where historical data do not exist, a documented testing and/or evaluation program designed to assess the stability characteristics of the excipient should

be undertaken. The results of such stability testing and/or evaluation should be used in determining appropriate storage conditions and retest or expiry dates. The testing program should include the following:

- the number of batches, sample sizes and test intervals,
- storage conditions for samples retained for testing,
- suitable stability-indicating test methods,
- storage of the excipient in containers that simulate the market container, where possible.

The stability of excipients may be affected by undetected changes in raw materials or subtle changes in manufacturing procedures or storage conditions. Excipients may also be shipped in a variety of packaging types that can affect their stability (for example, plastic or glass bottles, metal or plastic drums, bags, tank cars, or other bulk containers).

Some excipients may be available in different grades (for example, various molecular weights of a polymer or different monomer ratios, different particle sizes, bulk densities) or may be mixtures 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 types of excipients, a model product approach may be appropriate for assessment of the stability of similar excipients. 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 should be scientifically sound and documented. Data from stability studies of these model products can be used to determine theoretical stability for similar products.

Expiry/Retest Periods—An expiry or retest period should be assigned to each excipient and communicated to the customer. Common practice is to use a retest period rather than an expiry period.

Control of Nonconforming Product—Raw material, intermediate, or finished excipient found not to meet its specifications should be clearly identified and controlled to prevent inadvertent use or release for sale. A record of nonconforming product should be maintained. Incidences of nonconformity should be investigated to identify the cause. The investigation should be documented and action taken to prevent recurrence. There should be a documented procedure defining how the retrieval of an excipient from distribution should be conducted and recorded. Procedures should exist for the evaluation and subsequent disposition of nonconforming products. Nonconforming product should be reviewed in accordance with documented procedures to determine if it can be

- reprocessed or reworked to meet the specified requirements,
- accepted by the customer with customer agreement,
- regraded for other applications,
- destroyed.

Reprocessing—Repetition of an activity that is a normal part of the manufacturing process (reprocessing) should occur only when it has already been documented that the excipient may be made in that manner. In all other cases, the guidance for reworking should be followed.

Reworking—An activity that is not a normal part of the manufacturing process (reworking) should be conducted only following a documented review of risk to excipient quality and approval by the quality unit. As appropriate, when performing the risk assessment, consideration should be given to the following:

- new impurities that may be introduced as a result of reworking,
- additional testing to control the reworking,
- records and traceability to the original batches,
- suitable acceptance criteria for the reworked excipient,
- impact on stability or the validity of the reevaluation interval,
- performance of the excipient.

When the need to rework an excipient is identified, an investigation and evaluation of the cause are required. The equivalence of the quality of reworked material to original material should also be evaluated and documented to ensure that the batch will conform to established specifications and characteristics. Batches of excipients that do not conform to specifications individually must not be blended with other batches that do conform in an attempt to hide adulterated or substandard material.

Returned Excipients—Returned excipients should be identified and quarantined until the quality unit has completed an evaluation of their quality. There should be procedures for holding, testing, reprocessing, and reworking of the returned excipient. Records for returned products should be maintained and should include the name and the batch number of the excipient, the reason for the return, the quantity returned, and the ultimate disposition of the returned excipient.

Analysis of Data—The excipient manufacturer should develop methods for evaluating the effectiveness of its quality management system and use those data to identify opportunities for improvement. Such data can be derived from customer complaints, product reviews, process capability studies, internal audits, and customer audits. The analysis of such data may be used as part of the management review (also see above, *Management Review* under the *Management Responsibility* section). A periodic review of key indicators such as product quality attributes, customer complaints, and product nonconformities may be conducted to assess the need for improvements.

Improvement

Continual Improvement—The excipient manufacturer should take proactive measures to continuously improve manufacturing and quality management system processes. To identify opportunities for continual improvement, analysis of the following performance indicators may be considered:

- causes of nonconforming product,
- results of internal and external audits,
- customer returns and complaints,
- process and operational failures.

Corrective Action—The excipient manufacturer should establish, document, and maintain procedures for the following:

- determining the root causes of nonconformities,
- ensuring that corrective actions are implemented and effective,
- implementing and recording changes in procedures resulting from corrective action.

Preventive Action—The excipient manufacturer should establish, document, and maintain procedures for the following:

- initiating preventive actions to deal with problems at a level corresponding to the risks,
- implementing and recording changes in procedures resulting from preventive action.

APPENDIX 1. AUDITING CONSIDERATIONS

Introduction

Many excipients are used in food, cosmetic, and industrial products as well as in pharmaceuticals. Thus, environmental conditions, equipment, and operational techniques employed in excipient manufacture are often those of the chemical industry as opposed to the pharmaceutical industry. Chemical processes can produce impurities from side reactions. Careful process control is therefore essential to minimize levels of impurities and contamination.

Excipients are often manufactured on a large scale, using continuous processing and automated process controls. Production equipment and processes vary depending on the type of excipient being produced, the scale of production, and the type of operation (for example, batch versus continuous process).

This appendix is intended as an aid in preparing for an audit of an excipient manufacturer. Both external and internal auditors (see also *Internal Audit* in *Monitoring and Measurement* under the *Measurement, Analysis, and Improvement* section) will find this appendix useful in identifying the significant issues with respect to GMP and quality that require examination. This section will assist excipient manufacturers in identifying key deliverables when adopting the GMP standards listed in the other sections of this chapter; in planning an audit, it will also help to verify the quality of the excipient manufacturing process and the manufacturers quality management system.

GMP Principles

Control of Impurities and Contamination—In general, the pharmaceutical customer does not perform further chemistry or purification steps on the excipient; it is used as purchased. Consequently, impurities present in the excipient are likely to be present in the drug product. Although dosage form manufacturers have some control over excipient quality through specifications, excipient manufacturers have greater control over the physical characteristics, quality, and presence of impurities in the excipients they produce.

External contamination of the excipient can arise from the manufacturing environment. However, chemical processes used to manufacture excipients are often performed in closed systems that afford protection against such contamination, even when the reaction vessels are not located in buildings. The external environment may require suitable controls to avoid potential contamination wherever the excipient or in-process material is exposed.

Excipient Properties and Functionality—Excipients are frequently used in those types of drug products for which physical characteristics, such as particle size, may be important. Although the manufacturer of the finished dosage form is primarily responsible for identifying the particular physical characteristics needed, it is also the responsibility of the excipient manufacturer to control excipient manufacturing processes to ensure consistent conformity to excipient specifications. Wherever possible, consideration should be given to the end use of the excipient. This is particularly important if the excipient is a direct component of a sterile drug product or one that is claimed to be pyrogen-free.

Consistency of Manufacture and Change Control—A thorough understanding of the manufacturing process and effective control of change can best ensure consistency of excipient quality from batch to batch. Implementation of changes may also have consequences for registration filings with regulatory agencies.

Changes in excipient manufacturing processes may result in changed physical or chemical properties of the excipient that are evident only during subsequent processing or in the finished dosage form. This is particularly important in the context of the pharmaceutical product approval process where bioequivalence comparisons are made between pivotal, clinical trial batch (*bio batch*) production and commercial scale-up batches. Changes made to the excipient supplied for the commercial product from the excipient supplied for the bio batch should not affect the quality and performance of the commercial drug product. Scale-up of excipients to commercial production may involve several stages, and data may be required to demonstrate consistency between batches through the scale-up process.

Traceability—Traceability of batch-related records to facilitate investigations and retrieval of product is also a key requirement of GMP.

Application of GMP Principles

It is the responsibility of the excipient manufacturer to designate and document the rationale for the point in the manufacturing process at which appropriate GMP are to be applied. From this point on, appropriate GMP should be applied. The manufacturer should apply a level of GMP to each manufacturing stage commensurate with the importance of that step in ensuring product integrity. This may be demonstrated by means of the use of a risk assessment procedure (for example, HACCP, FMEA).

The stringency of GMP in excipient production should increase as the process proceeds from early manufacturing to final stages, purification, and packaging. Physical processing (for example, granulation, coating, or physical manipulation of particle size such as milling or micronizing) as well as chemical processing of excipients should be conducted at least to the standards suggested by this chapter.

It should be recognized that not all intermediates may require testing. An excipient manufacturer should, however, be able to identify critical or key points in the manufacturing process where selective intermediate sampling and testing are necessary in order to monitor process performance.

General Auditing Considerations

Audits of an excipient operation will be influenced by the purpose of the audit and the intended use of the excipient. The key stages of a production process should be examined to determine whether the manufacturer controls these steps so that the process performs consistently. Overall, an audit should assess the excipient manufacturers capability to deliver a product that consistently meets established specifications.

The audit team may consist of engineers, laboratory analysts, purchasing agents, computer experts, maintenance staff, and other personnel as appropriate to the scope and purpose of the audit. External auditors must respect the confidentiality of the manufacturers processes and other disclosures.

An audit should focus on the quality-critical processing steps that are necessary for producing an excipient that meets established physical and chemical criteria. These steps should be identified and controlled by the excipient manufacturer. Quality-critical processing steps can involve a number of unit operations or unit processes. Quality-critical steps can include, but are not limited to, the following:

- phase changes involving the desired molecule, solvent, inert carrier or vehicle (for example, dissolution, crystallization, evaporation, drying, sublimation, distillation, or absorption),
- phase separation (for example, filtration or centrifugation),
- chemical changes involving the desired molecule (for example, removal or addition of water of hydration, acetylation or formation of a salt),
- adjustments of the solution containing the molecule (for example, pH adjustment),
- precise measurement of added excipient components, in-process solutions, and recycled materials (for example, weighing or volumetric measurements),
- mixing of multiple components,
- changes that occur in surface area, particle size, or batch uniformity (for example, milling, agglomeration, or blending).

Audit Check Points

A good approach for an excipient plant audit is a review of the following areas:

- nonconformities—such as the rejection of a batch that did not meet specifications, customer complaints, return of a product by a customer, or retrieval of a prod-

uct. The manufacturer should have determined the cause of the nonconformity, prepared a report of the investigation, and initiated and documented subsequent corrective action. Records and documents should be reviewed to ensure that nonconformities are not the result of a poorly developed or inconsistent process;
- customer complaint files—such as reports that some aspect of the product is not entirely suitable for use, because such problems may be caused by impurities or inconsistencies in the excipient manufacturing process;
- change control logs—to ascertain whether the company evaluates its significant changes to decide whether the customer and/or regulatory authority should be notified;
- nonconforming products meeting or Material Review Board documents and/or equivalent records that demonstrate that the disposition of nonconforming product is handled in an appropriate manner by responsible individuals;
- master formula and production records for frequent revisions that may reveal problems in the excipient production process;
- evidence for the presence of unreacted intermediates and solvent residues in the finished excipient;
- materials management systems, to ensure adequate control over nonconforming materials so that they cannot be sold to customers or used in manufacturing without authorization;
- review of a process flow diagram, to aid understanding of the various processing stages. The critical stages and sampling points should be identified as part of the review of the processing records;
- review of contamination control measures.

In evaluating the adequacy of measures taken to prevent contamination and cross-contamination of materials in the process, it is appropriate to consider the following risk factors:
- the type of system (for example, open or closed). Enclosed systems in chemical plants often are not closed when they are being charged and/or when the final product is being emptied. In addition, the same reaction vessels are sometimes used for different reactions;
- the form of the material (for example, wet or dry);
- the stage of processing and use of the equipment and/or area (for example, multipurpose or dedicated);
- continuous versus batch production.

Documentation and Record Review

Documentation required for the early steps in the process need not be as comprehensive as in the latter stages of the process. It is important that a chain of documentation exist and that it be complete when the following is the case:
- the excipient can be identified and quantified for processes where the molecule is produced during the course of the process. For batch production, a theoretical mass balance may also be established with appropriate limits, because deviations from tolerance are a good indicator of a loss of control;
- an impurity or other substance likely to adversely affect the impurity profile or form of the molecule is identified, and subsequent attempts are made to remove it.

As chemical processing proceeds, a chain of documentation should be established that includes the following:
- a documented process,
- the identification of critical processing steps,
- appropriate production records,
- records of initial and subsequent batch numbers,
- records of raw materials used,
- comparison of test results against meaningful standards.

If significant deviations from the normal manufacturing process are recorded, there should be evidence of suitable investigations and a review of the quality of the excipient. Complete documentation should be continued throughout the remainder of the process for quality-critical processing steps until the excipient is packaged and delivered to the end user. The batch should be homogeneous within the manufacturers specifications. This does not necessitate the final blending of continuous-process material if process controls can demonstrate compliance with specifications throughout the batch.

In order to promote uniformity in excipient GMP inspections, the following basic requirements should be established:
- assignment of a unique batch number to the excipient, enabling it to be traced through manufacture to release and certification,
- suitable controls for the preparation of a batch record for batch processing and/or a production record, log sheet, or other appropriate documentation for continuous processing,
- demonstration that the batch has been prepared using GMP guidelines from the processing point at which excipient GMP have been determined to apply,
- confirmation that the batch is not combined with material from other batches for the purpose of either hiding or diluting an adulterated batch,
- records showing that the batch has been sampled in accordance with a sampling plan that ensures a representative sample of the batch,
- records showing that the batch has been analyzed using scientifically established test methods designed to ensure that the product meets established standards, specifications, and characteristics,
- stability data adequate to support the intended period of use of the excipient; these data can be obtained from historical data, from actual studies on the specific excipient, or from applicable model product studies that can reasonably be expected to simulate the performance of the specific excipient.

APPENDIX 2. GLOSSARY

The terms below are defined as used in this chapter. Wherever possible, definitions used by the International Conference on Harmonization have been used as the basis for the glossary.

Acceptance Criteria: numerical limits, ranges, or other suitable measures of acceptance for test results.

Active Pharmaceutical Ingredient (API): any substance or mixture of substances that is intended to be used in the manufacture of a drug product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of humans or animals.

Adulterated Material: a material that either has been contaminated with a foreign material or has not been manufactured using GMP. This does not pertain to a material that simply does not meet physical or chemical specifications.

Batch (Lot): a specific quantity of material produced in a process or series of processes so that it can be expected to be homogeneous. In the case of continuous processes, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

Batch Number (Lot Number): a unique combination of numbers, letters, and/or symbols that identifies a batch and from which the production and distribution history can be determined.

Batch Process: a process that produces the excipient from a discrete supply of raw materials that are present before the completion of the reaction.

Batch Record: documentation that provides a history of the manufacture of a batch of excipient.

Blending (Mixing): intermingling different conforming grades into a homogeneous lot.

Calibration: the demonstration that a particular instrument or measuring device produces results within specified limits by comparison with those produced by a reference or traceable standard, over an appropriate range of measurements.

CEP (Certificate of Suitability to the *European Pharmacopoeia*): certification granted to individual manufacturers by the European Directorate for the Quality of Medicines (EDQM) when a specific excipient or active ingredient is judged to be in conformity with a *European Pharmacopoeia* monograph.

Certificate of Analysis: a document listing the test methods, specification, and results of testing a representative sample from the batch to be delivered.

Commissioning: the introduction of equipment for use in a controlled manner.

Contamination: the undesired introduction of impurities of a chemical or microbiological nature or foreign matter into or onto a raw material, intermediate, or excipient during production, sampling, packaging or repackaging, storage, or transport.

Continuous Process: a process that continuously produces material from a continuing supply of raw material.

Critical: a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the excipient meets its specification.

Cross-Contamination: contamination of a material or product with another material or product.

Customer: the organization receiving the excipient once it has left the control of the excipient manufacturer; includes brokers, agents, and users.

Deviation: departure from an approved instruction or established standard.

Drug Master File (DMF): detailed information about the manufacture of an excipient that is submitted to the U.S. Food and Drug Administration (FDA).

Drug (Medicinal) Product: the dosage form in the final immediate packaging intended for marketing.

Excipient: substances other than the API that have been appropriately evaluated for safety and are intentionally included in a drug delivery system.

Expiry (Expiration) Date: the date designating the time during which the excipient is expected to remain within specifications and after which it should not be used.

Impurity: a component of an excipient that is not intended to be present but arises as a consequence of the manufacturing process.

In-Process Control/Testing: checks performed during production to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or excipient conforms to its specification.

Intermediate: material that must undergo further manufacturing steps before it becomes an excipient.

Lot: See *Batch.*

Manufacturer/Manufacturing Process: all operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, and storage of excipients and related controls.

Master Production Instruction (Master Production and Control Record): documentation that describes the manufacture of the excipient from raw material to completion.

Material: a general term used to denote raw materials (starting materials, reagents, and solvents), process aids, intermediates, excipients, packaging, and labeling materials.

Model Product: a product that represents a group of similar products with respect to composition, functionality, or specification.

Mother Liquor: the residual liquid that remains after crystallization or isolation processes.

Packaging Material: a material intended to protect an intermediate or excipient during storage and transport.

Production: operations involved in the preparation of an excipient from receipt of materials through processing and packaging of the excipient.

Quality Assurance: the sum total of the organized arrangements made with the object of ensuring that all excipients are of the quality required for their intended use and that quality systems are maintained.

Quality Control: checking or testing that specifications are met.

Quality-Critical: describes a material, process step or process condition, test requirement, or any other relevant parameter that directly influences the quality attributes of the excipient and that must be controlled within predetermined criteria.

Quarantine: the status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.

Raw Material: a general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or excipients.

Record: a document stating results achieved and/or providing evidence of activities performed. The medium may be paper, magnetic, electronic or optical, photographic, or another medium, or a combination thereof.

Reevaluation Date (Retest Date): the date when the material should be reexamined to ensure that it is still in conformity with the specification.

Reprocessing: repetition of an activity that is a normal part of the manufacturing process and that has been documented previously.

Retrieval: process for the removal of an excipient from the distribution chain.

Reworking: subjecting previously processed material that did not conform to standards or specifications to processing steps that differ from the normal process.

Specifications: list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described for a material.

Stability: continued conformity of the excipient to its specifications.

Top Management: person or group of people who direct and control an organization at the highest level. The highest level can be at either the site level or the corporate level and will depend on the way in which the quality management system is organized.

Traceability: ability to determine the history, application, or location that is under consideration: for example, origin of materials and parts, processing history, or distribution of the product after delivery.

Validation: a documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria.

⟨1079⟩ GOOD STORAGE AND SHIPPING PRACTICES

This general information chapter is intended to provide general guidance concerning storing, distributing, and shipping of Pharmacopeial preparations. It describes procedures to maintain proper storage environments for individual articles and to ensure a preparation's integrity, including its appearance, until it reaches the user. There is no change to any applicable requirements under Current Good Manufacturing Practices, approved labeling, state laws governing pharmacies, the USP *General Notices and Requirements,* or