⟨1197⟩ GOOD DISTRIBUTION PRACTICES FOR BULK PHARMACEUTICAL EXCIPIENTS

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SECTION 1. INTRODUCTION AND SCOPE

1.1 Introduction

Excipients are used in virtually all drug products and are essential to product performance and quality. Typically, excipients are manufactured and supplied so that they comply with compendial standards. The pharmaceutical excipient supply chain participants include manufacturers, distributors, brokers, suppliers, traders, transporters, forwarding agents, and repackagers. The quality of pharmaceutical excipients is affected by inadequate control of activities including distribution, packaging, repackaging, labeling, and storage. Improper or inadequately controlled trade and distribution practices can pose a significant risk to the quality of pharmaceutical excipients and can increase the risk of contamination, cross-contamination, adulteration, mix-ups, degradation, or changes in physical or chemical properties. To maintain the original and intended quality, all participants in the excipient supply chain should carry out their activities according to appropriate standards for good trade and distribution practices as discussed in this chapter.

[NOTE—The Appendix consists of definitions and acronyms.]

1.2 Scope

This general information chapter provides recommendations for those activities and practices that ensure good trade and distribution practices for pharmaceutical excipients in order to ensure their intended quality. These activities and practices include quality management, organization, documentation, premises, storage, equipment, stability, prevention of adulteration, importation, packaging, repackaging, labeling, dispatch, transport, returned goods, and compounding practices. In addition, personnel, authenticity of data, expiration dating, retesting, complaints and recalls, handling of nonconforming materials, internal/external/third-party audits, quality agreements, shelf life, traceability, economically motivated adulteration, and conformance to compendial monographs are included. The procedures outlined here are applicable to all persons and manufacturers involved in the handling of pharmaceutical excipients and apply to every step in the supply chain. This chapter covers all materials designated as, or intended for use as pharmaceutical excipients, beginning with the point in the manufacturing process at which the final excipient is designated for pharmaceutical use.

1.3 General Considerations

Manufacturers, distributors, users, regulators, and consumers expect pharmaceutical excipients to be manufactured, packed, stored, and transported in a manner that does not compromise their suitability for use in medicinal products for human or veterinary use. Because they are components of drug products, excipients are drugs within the meaning of the U.S. Federal Food, Drug, and Cosmetic Act (FD&C Act), and thus the U.S. Food and Drug Administration (FDA) definition of adulteration applies when an excipient is not fit for its intended use.

Excipients are a diverse group of materials. They can be of animal, mineral, synthetic, or vegetable origin, and they include materials that are solids, liquids, or gases. Excipients can be packed and transported in container sizes ranging from a few grams to a railroad tank car.

Because of their diverse nature and the number of ways in which excipients can be transported from the manufacturing site through the supply chain to the ultimate site of use, this general information chapter cannot provide exhaustive detail for specific materials and modes of transport. Rather, this chapter provides general guidance about what is expected of those people and organizations involved in the supply and distribution of pharmaceutical excipients intended for use in the manufacture of pharmaceutical finished products. Hence, there are instances when *USP–NF* chapters *Good Manufacturing Practices for Bulk Pharmaceutical Excipients* ⟨1078⟩, *Bulk Pharmaceutical Excipients—Certificate of Analysis* ⟨1080⟩, and ▲*Significant Change for Bulk Pharmaceutical Excipients* ⟨1195⟩ ▲ (CN 1-May-2021) provide a more detailed guide about what is expected in these specific areas.

Excipients also are used in a variety of industries. Although most drug substances typically are made exclusively for use in pharmaceutical finished products, the pharmaceutical use of an excipient may be only a small fraction of the total use of the material across all industries. This complicates the regulation of both the manufacture and the supply of pharmaceutical excipients. Excipients often are manufactured outside the United States, which further complicates the regulation of the manufacture and the supply of pharmaceutical excipients. Thus, all stages in the supply chain for the pharmaceutical excipient require transparency and proper flow of the necessary information regarding the excipient shipment. In addition, to ensure compliance with this chapter, suppliers of pharmaceutical excipients must follow all applicable national, regional, and local laws and regulations.

1.4 Pharmaceutical-Grade Excipients

Pharmaceutical excipients must be prepared according to the recognized principles of good manufacturing practices (GMPs) using ingredients that comply with specifications designed to ensure that the resulting substances meet the requirements of

the compendial monograph (see *General Notices, 3.10. Applicability of Standards* and chapter *Good Manufacturing Practices for Bulk Pharmaceutical Excipients* ⟨1078⟩).

USP or *NF* standards apply to any excipient marketed in the United States that is recognized in the compendium and is intended or labeled for use as an ingredient in a pharmaceutical product. The applicable standard applies to such articles whether or not the added designation *"USP"* or *"NF"* is used (see *General Notices, 3.10.10. Applicability of Standards to Drug Products, Drug Substances, and Excipients*). An ingredient may include the designation *"USP"* or *"NF"* in conjunction with its official title or elsewhere on the label only when a monograph is provided in the compendium and the article complies with the monograph standards and other applicable standards in the compendium including, but not limited to, the principles of GMP manufacture (see *General Notices, 3.20. Indicating Conformance*).

When *USP*- or *NF*-grade excipients are unavailable, manufacturers should first explore the use of materials which claim to comply with other pharmacopeias (e.g. EP, JP). If unavailable, pharmaceutical manufacturers should then consider appropriate alternatives (e.g. food-grade ingredients), provided such materials are suitable for the intended use. If a pharmacopeial grade is not used, a written justification should be available. The pharmaceutical manufacturer/user is responsible for the development and confirmation of suitable quality tests, procedures, and attributes to ensure that the material is appropriate for its intended use and that manufacturing is carried out under GMPs or a quality management system that demonstrates the same level of assurance of quality as that provided in *USP* (see ⟨1078⟩). It is an unacceptable practice to upgrade technical- or industrial-grade material to pharmaceutical-grade quality based only on analytical results that show compliance with the requirements of a pharmacopeial monograph.

1.5 Authenticity of Data

In the United States, the responsibility for the quality of the components of a finished pharmaceutical product lies with the organization that guarantees the quality of the finished pharmaceutical product. Thus, an important consideration in the purchase and supply of a pharmaceutical excipient is confirmation that the material is what it purports to be, that it meets specifications, that it was manufactured under applicable GMPs, that it has not been tampered with in any way before arriving at the site of intended use, that the appearance of the containers and other attributes of the shipment are comparable to those of previously received shipments of the same excipient and grade from the same supplier, and that it is fit for its intended use. Certain paperwork should accompany all shipments of pharmaceutical excipients. This paperwork should include a bona fide and legible copy of a Certificate of Analysis (COA) (see *Bulk Pharmaceutical Excipients—Certificate of Analysis* ⟨1080⟩).

When they receive a COA, manufacturers should take appropriate steps to verify the authenticity of the COA and the data contained therein. This has become particularly important in recent years because of instances of adulteration of excipients intended for use in the manufacture of pharmaceutical products. Steps to verify the authenticity of the COA should be taken at all stages in the supply chain.

Data on the COA can be verified in a number of ways, but the excipient user is responsible for confirming that the data are authentic by means of periodic verification of compliance with established specifications as stated in 21 Code of Federal Regulations Part 211 (21 CFR 211; see *Current Good Manufacturing Practice For Finished Pharmaceuticals*, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211, http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM095852.txt). In addition, other documents such as dispatch notes from previous stages in the supply chain can provide further evidence of the pedigree of the excipient shipment. Such documents are termed "pedigree documents".[1]

This chapter may present additional challenges for certain excipient users, e.g., compounding pharmacies. However, those who compound still are obliged to take all reasonable steps to verify that excipients they receive are fit for their intended use. Part of this verification can include an examination of pedigree documents and a signed certificate of conformance (COC) from the suppliers. Information contained in the *USP–NF* monograph's labeling requirements, FDA's Inactive Ingredient Database, and the CFR provide specific information about the excipient's permitted use in FDA-regulated products. All purchasers of pharmaceutical excipients should establish written procedures for the verification of data and verification that the excipient is fit for its intended purpose.

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SECTION 2: QUALITY, ORGANIZATION, AND DOCUMENTATION

2.1 Quality Management

A Quality Management System (QMS) is a tool by which all parties involved in the excipient supply chain maintain the quality of the excipient. A documented quality policy is the cornerstone of the QMS and formally describes the company's overall philosophy with regard to quality as authorized by top or senior management. Additionally, an appropriate QMS should include:

- An organizational structure capable of supporting the elements of the quality policy
- Documented procedures and relevant records that demonstrate that a product will meet established quality criteria. This is commonly known as quality assurance (QA)
- Established procedures for approving suppliers of starting materials and verifying that they continue to meet agreed-upon requirements
- A material-release testing procedure to confirm the quality of excipients for their intended purpose(s)

Excipient manufacturers and suppliers should prepare a Quality Manual. The Quality Manual describes the elements of the QMS and includes the quality organizational structure, written policies, procedures, and processes or references to them, and a

[1] IPEC. The IPEC Excipient Pedigree White Paper. Arlington, VA: IPEC; ND. Available at: http://ipecamericas.org/sites/default/files/Excipient_Pedigree.pdf (Accessed July 6, 2011).

description of departmental functions as they relate to the policies, procedures, and processes (see *Section 2.3 Documentation Requirements*). In implementing the QMS, companies must ensure that adequate qualified personnel are available to carry out the actions called for in the QMS and must avoid giving any one individual such extensive responsibilities that quality could be at risk.

COC to quality systems such as applicable International Organization for Standardization (ISO) guides or hazard analysis and critical control point (HACCP) analyses are not mandatory but provide assurance that products are produced and handled appropriately. However, certification to these quality systems should not be viewed as a substitute for the information contained in this chapter. In addition, internal audits should be conducted at regular intervals to confirm compliance with GMP (as applicable) and good distribution practices (GDP), and manufacturers should seek opportunities for improvement (see *Section 2.7 Audits: Internal, External, and Third-Party*).

All parties involved in the excipient supply chain share responsibility for the quality and safety of pharmaceutical excipients. These responsibilities should be delineated in a quality agreement between parties in the supply chain (see *Section 2.9 Quality Agreements*). All parties and their activities in the supply chain should be documented, and records should be maintained according to written procedures that ensure the traceability of all products acquired and distributed. All members of the supply chain have an obligation to protect excipients in their custody from deliberate economically motivated adulteration or deliberate introduction of foreign materials that could compromise the quality or performance of the excipient or adversely affect human or animal health.

2.2 Organization and Personnel

The organizational structure should be adequate and sufficiently staffed, and workers should be appropriately authorized for the activities they conduct. An organizational chart should delineate the responsibilities and interrelationships of personnel. Management ultimately is responsible for implementation of GDPs and ongoing verification that the QMS is maintaining the intended excipient quality.

Individuals within the company should have clearly defined responsibilities that are documented in writing. All individuals should understand their responsibilities and should be suitably qualified to perform their assigned duties. Their qualifications should be assessed for adequacy for their responsibilities and should be documented. Qualifications can include a combination of formal education, training, and experience. This also extends to any contracted service providers. Procedures should be in place to ensure that permanent, temporary, and contract employees minimize the possibility that unauthorized individuals will handle products.

An employee at each supply chain site should be designated and given the authority and responsibility for the implementation and maintenance of the QMS. The designated employee should have sufficient authority, qualifications, and resources to perform this function, as well as to identify and correct deviations from the QMS. Management and other personnel must not be subject to conflicts of interest or other pressures that could have an adverse effect on their ability to perform their duties related to product quality.

Staff should be aware of the principles of GDP included in this chapter and should receive regular, on-going training relevant to their responsibilities and to general quality principles. All training should be conducted according to a written training plan, and records of this training should be maintained. Personnel who have special duties such as handling hazardous materials or supervising activities required by local legislation may require additional training, including specific hazard management. Effectiveness of training should be verified regularly.

Personnel working with open product must understand and maintain good hygiene, health, and sanitation practices. Staff should use appropriate, nonshedding, protective apparel that will protect the product from the sampler as well as the sampler from the hazards of the product. Established procedures should eliminate the potential for product contamination by personal items such as jewelry, food, drink, or tobacco products. Written procedures that address hygiene, health, sanitation, and protective apparel should be in place.

Each supply channel party should have in place disciplinary procedures to address situations when personnel involved in the handling of products are suspected of or are implicated in inappropriate or illegal activities.

Some quality-related duties may be contracted to third parties, persons, or entities outside of the direct employ of the supplier. The delegation of these activities should be documented in a quality agreement or contract with the third party, and the organization should confirm compliance with the principles of GDP by conducting periodic on-site audits of these third parties. Delegation to a third party does not remove the organization's overall responsibilities for these activities.

2.3 Documentation Requirements

2.3.1 GENERAL

Organizations should have in place a system to control documents and data that relate to the requirements of the QMS.

2.3.2 QUALITY MANUAL

Organizations also should maintain a quality manual that describes the QMS, the quality policy, and the company's commitment to applying the appropriate GDP and quality management standards contained in this chapter. This manual should include the scope of the QMS, reference(s) to supporting procedures, and a description of the interaction between quality management processes.

2.3.3 DOCUMENT CONTROL

Procedures for the identification, collection, indexing, filing, storage, withdrawal, archiving, maintenance, and disposition of controlled documents, including documents of external origin that are part of the QMS, should be established and

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

Designated qualified personnel should review documents and subsequent changes to the documents before the latter are issued to the appropriate areas. Documents that influence product quality should be reviewed and approved by the quality unit. Controlled documents may include a unique identifier, date of issue, and revision number to facilitate identification of the most recent document. The department with the responsibility for issuing the documents should be identified. The reasons for changes and the implementation date should be documented.

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

2.3.4 CONTROL OF RECORDS AND DATA

Procedures for the identification, collection, indexing, filing, storage, maintenance, and disposition of records and data should be established and maintained. Records and data should be maintained to demonstrate achievement of the required quality and the effective operation of the QMS. Records and data should be legible and clearly linked with the product or process involved. Pertinent third-party quality data also should be an element of these records.

Entries in records and data should be clear and indelible and should be made directly after the person performs the activity and then should be signed and dated by the person who made the entry. Corrections to entries should be signed and dated, leaving the original entry legible and with an explanation for the change, especially if this may not be obvious to subsequent reviewers.

Records and data should be kept for a defined period that is appropriate for the excipient, its use, and its retest or re-evaluation date. Records and data should be stored and maintained in such a manner that they are readily retrievable and in facilities that provide a suitable environment to minimize deterioration or damage. Electronic records and automated data-capture systems should meet the requirements for controlled records and data as stated above.

2.3.5 CHANGE CONTROL

Procedures to evaluate and approve all changes, including evaluating the impact of the change on the quality of the excipient, should be established and maintained, for example, changes to the following:

- Authorized excipient manufacturer or packaging material supplier
- Manufacturing or packaging sites
- Excipient or packaging material specifications
- Test methods and laboratory
- Repackaging, labeling, and storage equipment
- Analytical equipment
- Repackaging, labeling, and storage processes
- Process and equipment changes at the original excipient manufacturer's site (see ▲*Significant Change for Bulk Pharmaceutical Excipients* ⟨1195⟩▲ (CN 1-May-2021))

An independent QA group should have the responsibility and authority for the final approval of any changes. The QA group may be part of another operational unit such as regulatory affairs or research and development.

Customers and, if applicable, regulatory authorities (e.g., those responsible for drug master files or certificates of suitability to the *European Pharmacopoeia*) should be notified of significant changes to established production and process control procedures that could affect excipient quality. The original manufacturer and downstream intermediaries (distributors and traders) should have excipient change control agreements in place defining the extent of notification by the original manufacturer in case of a change as described above. Each of the handling parties within the supply chain should have change control agreements to ensure that changes from the original excipient manufacturer are communicated to the end user. This change control agreement is part of the overall contractual agreements between the parties.

2.4 Complaints and Deviations

Customer complaints and information about possible defects should be systematically documented and investigated based on a written procedure with assigned responsibilities that describes the action that will be taken and includes the criteria on which a decision to recall a product should be based. Investigations should be formally conducted and written up in a timely manner to establish if the complaint is justified, to identify the origin or reason for the complaint (e.g., the repackaging procedure, the original manufacturing process, etc.), to identify root cause(s), to define any initial and follow-up action(s), and the method of communication (e.g., to the customer, original excipient manufacturer, authorities, etc.). Complaint records should be retained and regularly evaluated for trends, frequency, and criticality in order to identify possibly needed corrective or preventive actions.

Investigations should identify whether the reported defect is limited to a single batch of material or if other batches must be investigated. If additional batches are implicated, they should be identified and labeled accordingly (e.g., "under quarantine"). As necessary, appropriate follow-up action, possibly including a recall (as outlined in *Section 2.5 Recalls*), should be taken after investigation and evaluation of the complaint. Confirmed serious problems related to product quality (e.g., faulty manufacturing, packaging, or product deterioration) should be communicated upstream to the manufacturer and downstream to customer(s) in case they received material with the same batch number. A similar process should be implemented for the handling of deviations and product defects not identified by a customer complaint.

2.5 Recalls

Those involved in the excipient supply chain should have a system for recalling promptly and effectively any materials known or suspected to be defective. Entities involved in the supply chain should implement written procedures to manage excipient recall (retrieval) in a timely manner. The procedures should:

- Describe how the process of recall (retrieval) should be managed based on the risk involved
- Describe a decision-making process with defined responsibilities
- Define the functions involved in the process (e.g., QA, sales, logistics, senior management, competent authorities, etc.)
- Define the communication process and documentation to parties within the supply channel as well as to regulatory authorities
- Define the steps needed to retrieve the material

If the original excipient manufacturer does not initiate a recall, it should be informed of the recall. Entities in the supply chain should have written procedures for the organization of any recall activity, and these should be regularly checked and updated. All recalled materials should be stored in a secure, segregated (quarantined) area while their disposition is decided. In the event of serious or potentially life-threatening situations, all customers and competent authorities in all countries to which an excipient potentially was distributed should be promptly informed of any intention to recall the excipient. All records should be readily available to the designated person(s) responsible for recalls. These records should contain sufficient information about materials supplied to customers (including exported materials). At regular intervals, QA groups in supply-chain organizations should evaluate the effectiveness of recall arrangements.

2.6 Handling of Nonconforming Materials

Nonconforming materials should be handled in accordance with a procedure that will prevent their inadvertent introduction or reintroduction into the market. They should be stored separately, either physically separated or under electronic control, to prevent their inadvertent introduction into commerce. Firms that conduct recalls should maintain records covering all activities, including destruction, disposal, return, and reclassification, and should perform an investigation to establish whether any other batches also are affected. They should document the investigation and actions taken to prevent recurrence of the problem. As necessary, firms should take corrective measures. Procedures should exist for the evaluation and subsequent disposition of nonconforming products, and the disposition of the material, including downgrading to other suitable purposes, should be documented. Nonconforming materials should never be blended with materials that comply with specifications.

2.7 Audits: Internal, External, and Third-Party

To verify compliance with the principles of GDP for pharmaceutical excipients, firms in the excipient supply chain should perform regularly scheduled internal audits in accordance with approved procedures. Firms should document audit findings and corrective actions and ensure that they are brought to the attention of responsible management. Accepted corrective actions should be completed in a timely and effective manner and should be conducted by designated, qualified individuals. Qualified individuals may be employees of the company, but they must be sufficiently removed from the function under audit so that their independence is not compromised.

Firms should perform external audits in accordance with approved procedures and schedules to assess the capability of suppliers to meet requirements for a product or service, as specified. A response to a questionnaire may be considered in the auditing process but generally does not take the place of on-site inspections and should not be considered a substitute when an audit is required. Independent auditing organizations can perform third-party audits to determine the level of compliance or conformance to specified standards and regulations (e.g., GMP, GDP, and ISO).

2.8 Contract Activities

Any GDP-related activity that is delegated to another party should be agreed upon in writing in an approved contract with clearly defined responsibilities. The contract should clearly establish which party is responsible for each applicable quality activity. Before entering into an agreement, the contract giver should evaluate the proposed contract acceptor's compliance with GDP as described in this general chapter. The evaluation should include an initial on-site audit of the contract acceptor's premises and quality system, giving special consideration to the prevention of cross-contamination and maintaining traceability. The contract should also include the responsibilities of the contract giver for measures to avoid the entrance of counterfeit or adulterated materials into the distribution chain.

There should be no gaps or unexplained lapses in the application of GDP. The contract acceptor should conduct periodic on-site auditing of contracted distribution activities with regard to the application of GDP by the contract giver. Subcontracting may be permissible under certain conditions, subject to approval by the original contract giver, especially for activities such as sampling, analysis, repacking, and labeling. If subcontracting occurs, the subcontractor should conform to the same GDP standards as the primary contract giver. The subcontractor also should permit an on-site audit by the contract acceptor's quality unit or its designee.[2, 3]

[2] WHO. *Good Trade and Distribution Practices for Pharmaceutical Starting Materials*. Geneva; WHO: Technical Report Series, No. 917, 2003, Annex 2. Available at: http://who.int/medicines/areas/quality_safety/quality_assurance/GoodtradeDistributionPracticesTRS917Annex2.pdf?ua=1 (Accessed March 2, 2015).

[3] WHO. *Finished Products: Good Distribution Practices for Pharmaceutical Products*. Geneva; WHO: Technical Report Series 957, 2010, Annex 5. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_957_eng.pdf (Accessed July 7, 2011).

2.9 Quality Agreements

Quality agreements are legally binding and are mutually negotiated between parties involved in the supply chain for pharmaceutical excipients. The quality agreement identifies who is responsible for certain quality activities and how quality issues will be resolved between the parties. Although they are intended to address the parties' quality commitments, quality agreements are not designed to take the place of an audit.

Suppliers should have in place quality agreements between themselves and the parties with whom they do business. Original excipient manufacturers should have quality agreements in place with their direct customers and authorized distributors of their products. Distributors should also have agreements with end users and other parties in the supply chain to whom they supply products. All entities in the supply chain should fully understand which entity is responsible for the GDP-related activities (as outlined in this chapter) at each step in the supply chain.

Quality agreements should address the quality systems requirements, but they are not intended to list every element of the quality system. It is not necessary to reiterate agreement on every point of the quality system when the parties state general agreement on the applicable quality standard. Quality responsibilities included in a quality agreement should be those that may require action by one or both parties to the agreement.

A key element that must be defined in the quality agreement is the communication pathways and timing for quality events. Parties must be clear about their responsibility for notifying the next party in the supply channel and for notifying the applicable regulatory authorities in the case of a significant quality event. Many times a decision about who should notify the regulatory authority is a collaborative effort between the parties. Depending on the issue's impact, the timing of these notifications relative to the time of the incident should be specified within the quality agreement.

Both parties to the agreement are responsible for ensuring that the quality agreement is maintained as an accurate document throughout the life of the business relationship. Revisions to this document may be needed as regulatory requirements change, new products are supplied, or a new material risk arises. The parties should maintain a history of the revisions to the quality agreement.

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SECTION 3: PREMISES, STORAGE, REPACKAGING, AND STABILITY

3.1 Buildings and Facilities

Organizations should establish operating procedures for the use of buildings and facilities, including the areas discussed below, and firms should consider protective measures to ensure the security of the grounds (e.g., fencing or perimeter walls).

The buildings and facilities used in the storage and handling of excipients should restrict access to allow entrance only by authorized persons to areas used for the manufacture, packaging, and holding. Organizations should take precautions to prevent unauthorized persons from entering limited-access areas. When the status of excipients requires protection from use (e.g., quarantine), organizations must have clearly marked limited-access controls in place, or they should use validated computerized systems to prevent material distribution before approved release.

Buildings should be of adequate size and capacity to allow the orderly flow of materials, proper storage and handling of materials, and appropriately controlled environmental conditions for the final dispatch of excipients into and out of the premises. Buildings should be maintained in a good state of repair. The construction materials must be easily cleanable and maintained, and buildings and facilities should be designed to prevent cross-contamination, product mix-ups, or the accumulation of filth or contaminating materials, particularly when excipients are exposed to the environment. Adequate storage space must be available for excipients that are highly sensitizing or toxic, and dedicated facilities may be necessary. Adequate procedures should be in place to ensure the cleaning, maintenance, and use of buildings and facilities.

Receiving and dispatch bays should be designed to protect the facilities and excipients during loading and unloading during adverse weather conditions. Incoming bay areas should be designed and equipped to allow containers to be cleaned before storage. A pest-control system should be in place to ensure that materials are protected from infestation by insects, rodents, animals, birds, or other vermin. There should be written procedures defining the adequate holding and storage of excipients, including pest-control processes. The pest-control materials must be safe and must be known not to cause contamination. Approved pesticides, insecticides, and rodenticides should be used and documented. Excipients that may contain contamination must be controlled to prevent cross-contamination in holding areas or the spread of contamination to other areas of the facility.

3.2 Warehousing and Storage

Written procedures should describe the receipt, storage, dispatch, and other handling of excipients, as well as the security measures necessary to prevent theft of materials or the introduction of counterfeit or adulterated materials into the supply chain. Buildings should be adequately lighted and should have proper utilities for the intended activities. They should be dry and controlled to appropriate environmental conditions. Buildings and facilities should store excipients in the proper environmental conditions. Temperature-controlled and -monitored storage should be available as required for any building used for holding excipients.

Warehousing and storage conditions for excipients should comply with the monograph specifications, as reflected in the excipient's container label. When specific storage conditions are required for excipients (e.g., temperature and humidity control), they should be provided in a controlled manner, monitored (e.g., by an alarm system or manual control), and recorded. Any automated system(s) used to monitor the environmental conditions for areas where excipients are handled or stored must be validated. An approved document should indicate the location of each environmental monitoring device and the condition(s) it monitors. The locations for these devices or probes should reflect the extreme environmental conditions of the space as

determined by an environmental mapping exercise. Excipients that present risks such as fire or explosion should be stored in safe, dedicated areas. Excipients that are sensitizing or toxic should be adequately and appropriately segregated, and warehouse and storage areas should be routinely cleaned, appropriately maintained, and free of pests.

Excipients should be stored in a manner that permits cleaning of the storage area and movement of materials. Pallets used to hold materials should not cause contamination, and required pallet quality and construction materials should be defined in writing. Pallets should be clean and in a good state of repair, and firms should appropriately track supplies to ensure adequate treatment of the wood materials. Wood pallets, if used, should comply with import requirements.

Organizations should have in place written procedures to ensure that the excipient will be supplied within its expiry or retest period and should have adequate controls to prevent the distribution of expired excipients. If no expiry date is applicable, the first-in-first-out principle should be used. Rejected excipients and other materials related to excipient quality (e.g., packaging components) should be so labeled or identified, and controls such as physical or electronic separation should prevent their use pending final disposition. During the warehousing or storage of excipients, any known broken or damaged containers should be withdrawn from usable stock, and the containers should be handled as rejected materials.

Materials quarantined pending a release decision should be labeled or identified (e.g., electronically) to prevent unauthorized use. These materials should be held from use, and written procedures should guide final disposition. There should be written procedures for the cleanup of any spillage to ensure complete removal of any risk of contamination.

3.2.1 ENVIRONMENTAL CONTROLS

When excipients require specific storage conditions to preserve their integrity and quality during the retest/re-evaluation or expiry interval, the storage conditions required should be stated on the label, labeling, or other literature, e.g., the Excipient Information Package[4] or COA. Distributors should follow the information and requirements for environmental controls provided by the manufacturer and should provide appropriate controls and monitoring to ensure adherence to the stated storage conditions with appropriate documentation. Distributors should also maintain records to indicate the excipient was stored according to the manufacturer's recommendations and should conduct regular assessments to confirm that designated conditions are met.

If the manufacturer does not indicate specific storage conditions, the distributor should ensure that proper storage conditions are maintained to protect the packaging and labeling. Uncontrolled warehousing conditions vary with geographical location, particularly with latitude. If the excipient is shipped to geographical locations that have storage conditions well outside the conditions used in the manufacturer's stability study or justification for the absence of special storage conditions, then additional studies may be required to show stability at the new conditions. A warehouse-monitoring program should be established if the effects of the new environmental conditions are not known.

Outdoor storage of excipients (for example, bulk materials, flammable materials, acids, or other corrosive substances) is acceptable provided the containers give suitable protection against deterioration or contamination of their contents, identifying labels remain legible, discharge ports have adequate protective closures, and the exteriors of moveable containers are adequately cleaned before opening and use.

3.3 Equipment

Equipment used in bulk transport, repackaging, labeling, testing, or storage of the 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. Equipment should be verified before use to ensure that it is constructed, installed, and functioning as required for the excipient. When equipment is located outdoors, there should be suitable controls (e.g., closed systems or protective encasements) to minimize environmental risks to excipient quality.

When possible, dedicated equipment (e.g., bulk trucks, packaging equipment, storage tanks, pipework, hoses, and pumps) should be used in direct contact with the excipient. When nondedicated equipment is used in direct contact with the excipient, validated cleaning procedures should be applied. A restricted prior-cargo list should be supplied to transport companies in case non-dedicated bulk transport equipment is used. Quality-critical measuring equipment and balances for the handling and testing of the excipient should be of appropriate range and precision. Such equipment should be identified.

3.3.1 EQUIPMENT CONSTRUCTION

Equipment in contact with an excipient should be constructed so that contact surfaces are not reactive, additive, or absorptive and thus do not alter the quality of the excipient. Substances required for operation, such as lubricants or coolants, preferably should not come into contact with excipients and packaging materials. When contact is possible, distributors should use materials of suitable quality that will not affect product quality. The choice of such materials should be justified.

Equipment should be designed to minimize the possibility of contamination from the environment and direct operator contact during activities such as unloading bulk trucks, use of transfer hoses (particularly those used for transfer of excipients), sampling, repackaging, and cleaning. Distributors should consider the sanitary design of equipment in contact with excipients. They should assess the suitability and integrity of seals in order to minimize the risk of contamination. Piping should be appropriately labeled to indicate the content and direction of flow.

3.3.2 EQUIPMENT MAINTENANCE

Documented procedures should be established and followed for maintenance of critical equipment used in the repackaging, labeling, testing, or storage of the excipient. Distributors should maintain records (e.g., logs, computer databases, or other

[4] IPEC. *The IPEC Excipient Information Package (EIP): Template and User Guide*. Arlington, VA: IPEC; 2013. Available at: http://ipecamericas.org/reference-center/document-depot (Accessed June 23, 2017).

appropriate documentation) of quality-critical equipment use and maintenance. Defective equipment should be removed or appropriately labeled to avoid misuse.

Quality-critical measuring equipment and balances should be controlled on a scheduled basis. This control should include the following:

- Calibration of instruments or other appropriate verification at suitable intervals, according to an established documented program
- Establishment of the equipment's limits of accuracy and precision
- Provisions for remedial action in the event that accuracy or precision requirements are not met

Calibration standards should be traceable to recognized national or compendial standards as appropriate. Instruments and equipment that do not meet 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 or verification status of quality-critical equipment should be known to users and should be verifiable.

3.3.3 EQUIPMENT CLEANING

Cleaning equipment should be chosen and used so that it cannot be a source of contamination. Cleaning materials should be appropriate for the task, and their selection should be justified. Rotation of sanitizing and cleaning agents should be considered where appropriate. In order to avoid contamination with cleaning products or products previously processed in the equipment, written cleaning procedures should be established for equipment that comes in contact with the excipient. Cleaning procedures should contain sufficient detail to allow cleaning in a reproducible and effective manner. Cleaning and sanitation processes should be recorded, and evidence of their effectiveness should be provided, for example, by the following:

- Testing the final rinse after cleaning for residues of the previous product
- Checking the equipment after cleaning for residues of the previous product
- Testing each batch for residues of the previous product handled with the same equipment

3.4 Sampling, Repackaging, and Labeling

To minimize risks associated with repackaging and labeling, appropriate GMPs should be applied (see *Good Manufacturing Practices for Bulk Pharmaceutical Excipients* ⟨1078⟩). For completeness, certain key activities and the necessary precautions are discussed below.

3.4.1 BLENDING, REPACKAGING, AND LABELING

Operations such as combining sublots into a homogeneous batch, repackaging, or labeling are manufacturing processes, and therefore distributors should follow appropriate GMPs (see ⟨1078⟩):

- Processes whereby the excipient's packaging is opened and the excipient is exposed to the environment (for example, transferring excipient from one container to another, including from bulk equipment to storage tanks/silos or from storage tanks/silos into containers) are critical handling steps related to the integrity of the finished product. If only the secondary packaging is modified, operators should take appropriate care to maintain the integrity of the primary packaging and the excipient.
- Excipients may degrade because of exposure to the repackaging atmosphere (e.g., oxygen, humidity, light, and temperature).
- Excipients can be contaminated by foreign matter such as lubricants, cleaning materials, or other substances.
- Transparency to the customer that relabeling, with or without opening the original excipient manufacturer's packaging, has occurred is critical to representation of the product quality and suitability for use.
- Transparency to the customer of data sources listed on certification documentation (labeling) is critical to representation of the product quality and suitability for use.

3.4.2 REPACKAGING AND LABELING BATCHES

Staff in the excipient supply chain should give special attention to the following points:

- All repackaging and labeling requirements should be defined in written procedures.
- Contamination, cross-contamination, and mix-ups should be avoided by the use of suitable equipment and cleaning procedures and with adequate labeling.
- Environmental conditions and repackaging procedures should be designed to avoid contamination and to maintain the integrity of the excipient during repackaging and labeling.
- Operators should consider the use of filtered air in the repackaging area if necessary for the product. The standard of filtration should be justified.
- Labels should be printed using a controlled process (see *Section 3.4.9 Repackaging and Labeling*).
- Personnel involved in repackaging processes should wear clean protective apparel such as head, face, hand, and arm coverings, as necessary, and should practice appropriate personal hygiene (e.g., hand disinfection following health requirements, health monitoring, and removal of jewelry). Personnel should be trained about special hygiene requirements, and this training should be documented.
- Repackaging areas should be cleaned and sanitized regularly.

Batch numbers should be assigned according to documented procedures. When staff assigns new batch numbers, they should ensure traceability to original batch numbers by proper documentation. Assigning one batch number to containers of

different batches that comply with the same specification is an unacceptable practice (see also *Sections 3.4.3 Excipient Batch Homogeneity* and *3.4.4 Blended Excipients*).

- As part of the batch record, a copy of the information on the original labels should be retained (e.g., a photocopy). A sample of the new label should also be kept.
- All repackaging and labeling processes should be designed and carried out to avoid commingling, contamination, and mix-up and to ensure full traceability of the excipients back to the original excipient manufacturer and traceability downstream to the final customer. Responsible personnel should sufficiently record every completed step, along with the name of the operator and the date and time each step was completed, e.g., in the master batch manufacturing record, or by means of computerized systems.

3.4.3 EXCIPIENT BATCH HOMOGENEITY

Mixing to form a homogeneous batch is a manufacturing step and should be defined in a written procedure. A batch can be homogeneous only when conforming materials are thoroughly mixed. The conformity of each batch with its specification should be confirmed before it is added. Mixing should always be controlled, and homogeneity should be verified and documented (see *Good Manufacturing Practices for Bulk Pharmaceutical Excipients* ⟨1078⟩). Blending of batches or lots of excipients that individually do not conform to specifications with other lots that do conform (in an attempt to salvage or hide adulterated or expired material) is not an acceptable practice. Only excipients from the same manufacturing site received by a distributor and shown to conform to the same specifications can be mixed. The customer should be informed that the material supplied is a mixture of the manufacturer's batches.

3.4.4 BLENDED EXCIPIENTS

The blending process should be verified to ensure that it does not influence the quality of the excipient. The blended excipient should be tested to ensure conformance to the specification and to provide data for the COA (see ▲*Significant Change for Bulk Pharmaceutical Excipients* ⟨1195⟩▲ (CN 1-May-2021)). Under certain circumstances and with appropriate controls, a COC can be used if the basis for the claim of conformity is traceable within the document. The blended batch referred to in the new certification document should be traceable to all the original certification documents and batch numbers (see ⟨1078⟩).

3.4.5 CERTIFICATES OF ANALYSIS

The original excipient manufacturer's COA should be retained and made available to the user on request. The batch referred to in the COA delivered to the end user should be traceable to the original excipient manufacturer's COA. Quality documents accompanying deliveries should be subject to an agreement between the distributor and the final customer. For retesting, analytical methods of the original excipient manufacturer or pharmacopeial methods should be applied. When other methods are applied, these should be agreed upon by both parties.

3.4.6 CONTAINER–CLOSURE SYSTEMS

For repackaged material, the repackager is responsible for justifying the shelf life and repackaging conditions. The original manufacturer and the distributer should share information and agree about repackaging conditions and primary packaging materials. They should establish primary container–closure system material and packaging configuration specifications, and they should develop a written procedure that clearly defines packaging for each individual excipient based on its stability.

If the same types of primary container–closure system and packaging configuration are used for repackaging, then the new container–closure system and packaging configuration should be equivalent to that used by the original excipient manufacturer. The repackager and distributor should consider exposure of the excipient to the repackaging environment, and both can rely on the manufacturer's stability evaluation and thus assign the same shelf life for the excipient.

When the repackager's primary container–closure system's packaging configuration differs significantly from that of the original manufacturer [e.g., in terms of desiccants, permeability of the protective barrier layer (which may be either the primary or secondary container–closure system), or the headspace], the repackager must demonstrate that the new system is adequate to protect the excipient from contamination and deterioration for the shelf life (retest or expiration period) defined by the excipient manufacturer. Otherwise, the shelf life defined by the manufacturer cannot be transferred to the repackaged material. The need for stability studies should be confirmed (see *Sections 3.4.14 Stability and Expiration Dates* and *3.5 Retesting and Shelf Life*).

The container–closure system for the pharmaceutical excipient should protect the material from the time of packaging until its final use by the drug product manufacturer. The container–closure system should be designed to help prevent theft or adulteration by counterfeiting.

Storage and handling procedures should protect containers and closures and minimize the risk of contamination, damage or deterioration, and mix-ups (e.g., between containers that have different specifications but are similar in appearance).

3.4.7 RETURNED AND REUSED CONTAINERS

Returned containers may have unknown residues from uses other than the intended one. Therefore, use of new containers is recommended for excipients. If containers are reused, a rationale for the extent of cleaning should be justified and documented for specific excipients and different types of containers. Repackagers should collect evidence that the quality of the material packed is not adversely affected by reuse of containers.

Distributors and customers should have an agreement defining the specific conditions for reuse (e.g., handling, sealing, and cleaning). If returnable excipient containers are reused, all previous labeling should be removed or obliterated.

3.4.8 ENVIRONMENTAL CONTROLS

Environmental controls should ensure that temperature, humidity, and cleanliness of air and equipment are appropriate to avoid any contamination to or deterioration of the excipient. The necessary environmental conditions for the repackaging of each excipient should be defined. Environmental control is a specialist subject, and experts should be consulted (see also *Section 2.6 Handling of Nonconforming Materials*).

3.4.9 REPACKAGING AND LABELING

Repackagers should implement procedures to ensure that the correct quantity of labels is printed and issued and that labels contain the necessary information. Sufficient crosschecks should be in place to ensure proper data transfer. Procedures should be in place to avoid mislabeling, and printing and use of labels should be restricted. All labeling operations (e.g., generating, printing, storage, use, and destruction) should be recorded. Labeled containers should be inspected, and surplus labels should be destroyed to avoid any misuse. If labels are not printed immediately before each specific labeling operation, the security of the label stock should be controlled, and access limitations should be defined. Repackaging and labeling facilities should be inspected immediately before use to ensure that all materials that are not required for the next repackaging operation have been removed.

3.4.10 REPACKAGED EXCIPIENTS—ACCOMPANYING DOCUMENTATION

Deliveries of repackaged excipients should be accompanied by information about the original manufacturing site (name and address) and repackaging and labeling sites. This information should be provided in the supplier certification documentation (e.g., COAs) or by other means (see *Section 4.8 Traceability*). The supplier should provide this information to the customer via official communications.

3.4.11 TESTING OF REPACKAGED EXCIPIENTS

Appropriate testing of repackaged excipients should be performed to demonstrate consistent excipient quality. Testing to the complete monograph may not be necessary, but the recipient should test defined key quality parameters that could be affected by the repackaging process. Recipients should consider the manufacturer's recommendations for key quality parameters, and until these tests have been performed the repackaged materials should be kept under quarantine and should be identified as quarantined material. The materials should comply with the defined specifications before they are released for distribution.

Excipient testing and release should be performed under the responsibility of the quality unit and should conform to written specifications and analytical test requirements. Repackagers should ensure that test data are recorded and that results are evaluated before release of the repackaged or transferred excipient.

The excipient cannot be upgraded as a result of any repackaging process. It is unacceptable to upgrade nonpharmaceutical grades to pharmaceutical grades on the basis of conforming analytical results, i.e., by testing to pharmacopeial standards. Pharmaceutical grades can be achieved only when the excipient is originally produced and subsequently processed in accordance with GMPs (see *Good Manufacturing Practices for Bulk Pharmaceutical Excipients* ⟨1078⟩).

3.4.12 OFFICIAL PHARMACOPEIAL METHODS FOR RETESTING

For control of key parameters during repackaging or full retesting of excipients, official pharmacopeial methods or methods validated against the pharmacopeial methods should be used. Otherwise, repackagers should use the original excipient manufacturer's analytical methods. The methods used should be listed on the COA accompanying the excipient or should be made available to the customer by other documents. These documents should also reference any contract laboratory that is used to perform analyses. The COA should clearly identify which tests have not been performed on the repackaged or transferred batch but have been taken from the original manufacturer's COA.

3.4.13 SAMPLING

Excipient sampling must be done in a manner that prevents contamination, and dedicated sampling areas with adequate environmental controls are necessary. Areas for sampling should be designed to allow cleaning of the outside of the container before the container is opened. Adequate cleaning procedures should be in place for the sampling areas. Sampling tools should be dedicated to the sampling area and also to the specific material, or sampling tool cleaning must be validated to ensure no cross-contamination from the tool.

Any container opened for sampling should be marked with the date and name of the person who performs this operation. The amount of sample removed should be recorded.

If excipients are repackaged, processed, or packaged from bulk, retained samples representative of the excipient batch should be kept for at least one year after the expiration or re-evaluation date or for at least one year after distribution is complete, whichever is longer. The minimum sample size should be based on the amount required to perform at least two complete analyses. Sample storage conditions should prevent any contamination or deterioration and should comply with the label storage conditions (see general information chapter, *Bulk Powder Sampling Procedures* ⟨1097⟩).

3.4.14 STABILITY AND EXPIRATION DATES

Excipient stability and expiration dating of excipients are primarily the responsibility of the original manufacturer. Whenever the original manufacturer's packaging is opened, the repacker is responsible for providing evidence that the excipient manufacturer's stability and expiration dating are still applicable.

If a distributor transfers an excipient to another container or repackages it, stability and shelf life (retest or expiry period) should be taken into account. The type of container, primary packaging materials, barrier packaging materials, packaging configuration, environmental exposure during repackaging, and storage conditions at the repackaging site should also be taken into account when the shelf life (retest or expiry period) is defined. The recommended expiration date provided by the original excipient manufacturer should not be extended without demonstrating sufficient stability to justify extended shelf life (retest or expiry period). If shelf life is extended beyond the original manufacturer's recommendation, the type of packaging, storage conditions, and stability-indicating analytical data should be clearly defined, and the repacker assumes the primary responsibility for the extension.

If special storage conditions (e.g., inert gas overlay, protection from light, heat, moisture, etc.) are needed, the restrictions should be indicated on the new labeling (see *Section 3.5 Retesting and Shelf Life*).

3.5 Retesting and Shelf Life

The organization's stated shelf life or retest/re-evaluation interval should be maintained for the excipient. Expiration or shelf life dates indicate the period beyond which the excipient should not be used or distributed. Retest/re-evaluation intervals indicate the period beyond which the excipient must be evaluated to determine continuing acceptability for use. The expiration/shelf life date provided by the original excipient manufacturer should not be extended without documentation from the manufacturer demonstrating sufficient stability to justify an extended shelf life. Such documentation should specify the type of container and storage conditions necessary to make this claim, and the distributor should have documentation that the excipient was stored in the stated container and under the necessary conditions.

Excipients without expiration, retest, re-evaluation, or shelf life dates should be accepted for use only if the manufacturing date can be confirmed and only if the excipient has been held and shipped under conditions that conform to the appropriate standards of GMP or GDP. Distribution of the excipient beyond the retest/re-evaluation period should be done only in consultation with the manufacturer and with the consent of the purchaser or recipient. If the distributor has the capabilities for sampling and performing the manufacturer's specified evaluation, then the distributor can perform the assessment. Sampled lots should be placed under quarantine to prevent shipping during the evaluation.

Distributors who do have capabilities for sampling according to the manufacturer's instructions but do not have testing or evaluation capabilities should send the samples to the manufacturer or a qualified third-party laboratory for retesting/re-evaluation. Excipient lots that conform to the manufacturer's criteria can be released from quarantine, and the distributor's supporting evaluation data should accompany the original excipient manufacturer's data to indicate the excipient's acceptability for use. If the distributor does not have the capability to sample or evaluate the excipient, it should not be shipped to customers beyond the end of the retest/re-evaluation interval. The excipient or a representative sample of the excipient can be returned to the manufacturer or a third party for retesting/re-evaluation. The excipient can be held by the distributor pending further results obtained from the representative sample.

If an excipient is transferred to another container or is repackaged by the distributor, the latter must conduct an assessment of the stability of the excipient to determine if the original excipient manufacturer's information can be carried forward. If the distributor uses the same type of packaging material that provides the same packaged environment (headspace, surface area, closure tightness, etc.) as that used by the original manufacturer and if the transfer or repackaging is performed in a manner that protects the excipient from adverse environmental effects that could affect the stability, then the original excipient manufacturer's shelf life/expiry date or retest/re-evaluation interval can be carried forward. If primary packaging material or barrier packaging material differs from the original excipient manufacturer's primary packaging material or if the packaged environment varies significantly, then an evaluation of the container and its closure system should demonstrate that it is adequate to protect the excipient from deterioration and contamination during the manufacturer's shelf life/expiry date or retest/re-evaluation interval. Otherwise, a stability assessment is necessary to determine the appropriate shelf life/expiry date or retest/re-evaluation interval for the repackaged excipient. Such assessments should be conducted according to the manufacturer's specifications and test methods.

3.6 Expiration Dates

Not all excipients have an expiration date, but if one is assigned it should be displayed on the container and should show the period during which the excipient is expected to remain within specifications if stored properly and after which it should not be used. It is established for every batch by adding the shelf life to the date manufacturing began. The expiration date is based on the type of container and storage conditions, so these parameters should be clearly defined. If special storage conditions are needed (e.g., protection from light, oxygen, heat, humidity, etc.), they should be indicated on the labeling because they could influence usability through the expiration date.[5]

The expiration dates for excipients should be established by documented stability tests or long-term stability data. Occasionally, the expiration date may be established by reference to historical data. Stability involves not only the compendial requirements but also changes in performance properties. Excipient stability tests should determine whether possible degradation, changes in molecular weight and distribution, moisture gain or loss, viscosity changes, microbiological contamination, or other possible changes in excipients could occur when the excipient is stored in a specific container–closure type at specific storage conditions. Stability for repackaged excipients can be found under *Section 3.5. Retesting and Shelf Life*.

[5] IPEC. *The IPEC Excipient Stability Program Guide 2010*. Arlington, VA: IPEC; 2010. Available at: http://ipecamericas.org/reference-center/document-depot (Accessed June 23, 2017).

3.7 Labels, Icons, and Labeling

3.7.1 LABELS AND ICONS

Label-generating systems and processes should be secure, controlled, and documented. Appropriate verification records should be maintained, and each container should be appropriately identified and labeled. Labels applied to individual small containers should be clear, unambiguous, and permanently fixed in the company's established format. The information on the label should be indelible. Alternative methods can be used for bulk containers/transport and should be justified.

The label may include wording or depict icons to highlight storage and transportation handling requirements and hazards (e.g., avoid dropping, maintain specified environmental conditions, etc.). The use of symbols that are recognized by international organizations is recommended (see *Risks and Mitigation Strategies for the Storage and Transportation of Finished Drug Products* ⟨1079⟩). During international distribution, the proper language(s) should be used to ensure that handlers understand the requirements set forth on the label.

3.7.2 LABELING

The labeling (which includes both the label and any accompanying documents) should include at least the following information:

- Name of the excipient, including grade and reference to pharmacopeia, as relevant
- If applicable, the International Nonproprietary Name
- Amount (weight or volume)
- Batch number assigned by the original excipient manufacturer or the batch number assigned by the repacker if the material has been repacked and relabeled
- Retest date or expiry date (as applicable)
- Any specified storage conditions, as applicable
- Handling precautions, where necessary
- Identification of the original manufacturing site as agreed with the pharmaceutical customer (see *Section 4.8 Traceability*)
- Name and contact details of the suppliers

Change to read:

SECTION 4: RETURNED GOODS, DISPATCH, TRANSPORT, IMPORTATION, ADULTERATION, AND TRACEABILITY

4.1 Returned Goods

4.1.1 GENERAL

Return of goods by users to suppliers should be reviewed on a case-by-case basis. The distributor should facilitate a root cause analysis and investigation of complaints.

[NOTE—Users should document the reason(s) for return of goods to the supplier.]

Before returning the goods, if the user identifies and confirms unacceptable product quality the user should provide the supplier with the user's supporting documentation, such as tests and investigation results. If requested, the user should also provide product samples used for tests and investigations. The supplier should be provided an opportunity to conduct thorough investigations to confirm the validity of the user's quality complaint. While the investigation proceeds, the user should quarantine the material in accordance with internal standard operating procedures and should store the material in an area specifically designated for returns, with limited access to operations, and well-separated from incoming or released raw materials.

Goods returned by the user because of excess inventory or other causes unrelated to quality can re-enter commerce within the specified shelf life, provided conditions of storage, transportation, and container integrity have been thoroughly reviewed by the supplier and the quality of the excipient has not been compromised in any way. A formal documented review of each returned container and container tamper-evidence device should be done to verify that these match the container configuration when the materials left the supplier's facility.

If the user opens a commercial packaging container for sampling or investigation (related or unrelated to quality issues) and whether any material was taken out or not, each container should be clearly labeled *Opened*. Written documentation should be provided to the supplier confirming that the container(s) were opened and resealed according to GMPs and describing the reasons for opening, amount withdrawn, and how the pack/container was resealed. Documentation of returned goods should contain a detailed description of all such events including repackaging. Returned excipient containers opened by the user should be clearly identified as such and should not be released as pharmaceutical excipients. In exceptional cases, the material can be released as excipient-grade product if a documented thorough investigation shows no risk of product contamination or deterioration. The quality department should release this material.

Users and suppliers should maintain records of all returned goods, including the product name (trade name and chemical name), batch or lot number, reason for the return, quantity returned, and investigation documentation when applicable. In addition, the supplier should record the final disposition of the material. If returned excipients have been held, stored, or shipped under conditions that could compromise product quality (including ingredients, containers, or labeling), the manufacturer

should destroy the excipients. Exceptionally, manufacturers can release the excipients if their examination, testing, and investigations prove that the material meets suitable standards of identity, quality, and purity and that GMPs and GDPs have not been compromised.

4.1.2 DISPOSITION OF RETURNED GOODS

The excipient manufacturer's and/or supplier's quality unit should assess the returned product. The options are the following:

- Return to commerce
- Reprocess
- Regrade to a less stringent standard such as technical or industrial grade (non-GMP use)
- Destroy

Only containers that have not been opened should be considered for return to commerce without further action.

If the quality assessment of returned goods leads to their final destruction and if associated batches are potentially implicated, an appropriate investigation should be conducted and documented to show that the quality of the associated batches is not affected.

4.1.3 REPROCESSING

Reprocessing is a manufacturing step, and the requirements of *Good Manufacturing Practices for Bulk Pharmaceutical Excipients* ⟨1078⟩ apply. The requirements of ⟨1078⟩ apply only to those intermediate supply chain entities that undertake reprocessing.

4.2 Shipping and Transportation

4.2.1 SHIPPING

The supplier (the manufacturer or distributor) of pharmaceutical excipients should ensure that the integrity of the pharmaceutical excipient is maintained by the appropriate storage and transport conditions as described in product labeling. After training, staff should follow written procedures for shipping pharmaceutical excipients. These procedures include the requirement to follow the recommended storage and transportation requirements including temperature, humidity, or other special handling precautions.

Actions should be documented when they are performed. Shipping records for pharmaceutical excipients should provide for the following information:

- Date of shipment
- Name and address of the entity that accepted the materials for the transportation
- Mode of transportation
- Name, address, and status of the consignee
- Material name
- Quantity shipped
- Batch number and expiry date
- Required storage and transport conditions (refrigeration, freezing, or controlled room temperature required)
- Shipping code or identification number of the delivery order

When regulatory actions such as FDA Field Alerts or drug product recalls occur, the excipient handler must be prepared to act promptly. Shipping documentation must be sufficient to allow adequate handling of any excipient associated with regulatory action. When reasonable, the shipping schedule for excipients should be documented, and responsibilities can be enumerated in a quality or collaborative agreement between entities to show ownership in the supply chain (Entity A to Entity B; Entity B to Entity C; etc.—see *Section 4.4 Packaging: Tamper-Evident Seals*). The buildings and facilities used to ship materials should be appropriate for their intended use in the storage and handling of excipients (see *Section 3.1 Buildings and Facilities*).

Before loading materials, shippers should inspect the container and vehicle to ensure cleanliness and other consignments (if the shipment is a part load) to ensure no form of contamination is likely to occur. This inspection should be documented according to a written procedure. Materials should not be offloaded into other containers or vehicles without the written permission of the material owner or consignee.

4.2.2 TRANSPORTATION

Materials should be transported in a manner that will ensure the maintenance of controlled conditions as specified by the manufacturer. The transport process should not adversely affect the materials or integrity of the packaging. The supplier of transport services must be provided with the required information in order to maintain specified conditions.

The pharmaceutical excipient manufacturer or supplier should agree with the purchaser for arranging transportation. The need for temperature-controlled storage and transport should be determined using a risk-based approach, taking into account the nature of the excipient, results of stability assessments available from the excipient manufacturer or repackager, the supply chain, and the potential risks to the excipient. If temperature-controlled transportation is contracted, the shipper must have a mechanism for noting and reporting temperature excursions. Labeling on containers and transportation documents should detail the environmental conditions in a manner that provides the transporter or receiver with knowledge and immediate identification of these conditions, if required. The responsibility for ensuring that the proper storage conditions are met rests with each entity that handles, stores, or transports the materials.

Pharmaceutical excipients should be stored and transported in such a way that the identity and integrity of the material are retained, the material does not contaminate and is not contaminated by other materials, and adequate precautions are taken

against spillage, breakage, misappropriation, and theft. The required storage conditions for pharmaceutical excipients should be maintained within acceptable limits during transportation.

Excipients that are potentially dangerous because of the risk of fire or explosion (e.g., combustible liquids, solids, and pressurized gases) should be stored and transported in safe, dedicated, and secure areas, containers, and vehicles. In addition, applicable international agreements and federal regulations should be followed.

4.3 Tampering or Damaged Materials

Materials that are suspected of being tampered with or damaged must be quarantined immediately, and the manufacturer or distributor should be notified. The disposition of the quarantined material should be determined by the excipient manufacturer or supplier, after consultation with the customer. The excipient may be returned to the manufacturer or supplier. Alternatively, arrangements could be made for local certified destruction of the quarantined material. The supplier should make every effort to prevent these materials from being used until an investigation is completed and the final disposition of the material is determined. Written procedures should guide treatment of excipients that have been tampered with or the identification and handling of damaged material.

4.4 Packaging: Tamper-Evident Seals

A tamper-evident package has one or more indicators or barriers to entry that, if breached or missing, can reasonably be expected to provide visible evidence that tampering has occurred. To reduce the likelihood of successful tampering and to increase the likelihood that any breach will be discovered, the package should be distinctive by design or should employ one or more indicators of or barriers to entry. The term *distinctive by design* means that the packaging cannot be duplicated with commonly available materials or by commonly available processes.

A tamper-evident package may involve an immediate container–closure system in direct contact with the contents (primary packaging), a secondary container–closure system not in direct contact with the contents (secondary packaging), or any combination of systems intended to provide visual evidence of package integrity. For primary packaging in direct contact with the excipient (e.g., paper bags), any leak or break should be considered tampering even if the leak or tear is simply accidental damage. For excipients shipped in bulk, using, e.g., tank cars or containers, other means may be appropriate. However, whatever methods are adopted should provide adequate assurance as to the integrity of the excipient being shipped.

Visual examination of the packaging at each stage in the supply chain should provide evidence of repackaging or tampering with commercial packaging. In addition, the manufacturer's name and address, net weight of the material, material name, batch or packaging number, date of manufacture, and date of retest should be identified on a packaging label. The label should be prominently placed on the package and should be unaffected if the tamper-evident feature of the package is breached or missing.

The tamper-evident feature for excipient packaging should be designed so that it remains intact when handled in a reasonable manner from the time of packaging at the site of manufacture and throughout the supply chain—including but not limited to warehouse storage during various phases of the supply chain, transport, distribution, receipt, and storage at the user's facility until use for drug product manufacture.

The manufacturer should communicate tamper-evident features to the downstream members of the supply chain. If the latter observe any evidence that the tamper-evident feature or other part of the package has been compromised in any way, they should quarantine the material immediately and inform the supplier. Appropriate arrangements should be made with the supplier to return the material promptly with a description of the packaging breach. Alternatively, arrangements can be made by the excipient manufacturer or supplier for the local certified destruction of the quarantined material. The user should ensure adequate protection of the breached packaging during shipment to the supplier and can send photographs of the breached packaging to aid the supplier's investigation.

The supplier is responsible for the integrity of packaging, including but not limited to its tamper-evident features, until ownership of the commercial packages is transferred to the user. Material returned because of breach in packaging should be thoroughly reviewed and investigated by the supplier. The material should not be returned to commerce until the supplier has established that the integrity, identity, quality, purity, and safety of the excipient have not been compromised. The documentation requirement should comply with GMP expectations as well as elements of documentation and investigation suggested in *Section 4.1 Returned Goods*.

4.5 Where Ownership Begins

The excipient user is responsible for purchased materials throughout the supply chain. The supply chain qualification is documented by audits and COAs for all parties involved in trade and distribution of the materials. Such supply chain qualification and documentation supports the Excipient Pedigree and ownership of the excipient. The pedigree includes documentation of suitable excipient GMPs applied by the excipient manufacturer and suitable GDPs.

Ownership of the materials begins with the original excipient manufacturer and transfers to an intermediary or customer according to agreed-upon terms for insurance costs, transportation, and risk assumption. Such agreements are defined according to International Chamber of Commerce terms (Incoterms).[6] Incoterms are a series of international sales terms that are used to divide transaction costs and responsibilities between buyer and seller and reflect state-of-the-art transportation practices.

[6] International Chamber of Commerce. Incoterms. http://www.iccwbo.org/incoterms (Accessed June 6, 2011).

4.6 Adulteration

4.6.1 ADULTERATION

Adulteration is defined in the FD&C Act and 21 CFR in Sections 501(a)(2)(B) and 501(b)[7] and 21 CFR 211 for finished pharmaceuticals and Sections 402(a)(3) and (4)[8] and 21 CFR 110 for human food, and in 21 CFR 111 for dietary supplements. These laws and regulations establish the minimum current GMP (cGMP) necessary to prevent adulteration for finished pharmaceuticals, food products, and dietary supplements, respectively. Excipients for pharmaceutical use must be manufactured under appropriate GMPs and must meet the required chemical and physical specifications. In addition to specifications, excipient manufacturers and users have generally agreed quality attributes and limits defined by regulatory agencies, common industry practices, and pharmacopeial expectations. Adulteration or contamination of the products can be monitored and detected by many means including, but not limited to, compliance with these predefined quality expectations.

Adulteration can occur when any possible contamination of a product takes place, e.g., from foreign materials or undesirable microorganisms. The problem of adulteration can be addressed by standard practices supporting cGMPs, such as HACCP, Standard Operating Procedures, and staff training to control product safety and purity. This type of adulteration is the unforeseeable and unintentional type that can be controlled and, at worst, detected before the product leaves the manufacturer's site.

FDA specifies that a product can be considered adulterated when conditions *may* lead to adulteration because it is impossible to test every product for every conceivable contaminant. The safety and purity of substances require that manufacturers should build quality controls into the process rather than relying on QC testing.

4.6.2 INTENTIONAL ADULTERATION

Compared to unintentional adulteration, intentional adulteration is more specific because it requires a willful and knowing violation of regulations and standards designed to protect end user safety. It is the deliberate adulteration of an excipient. When an excipient is deliberately adulterated by substituting a lower-cost material for a material of higher cost, it is considered economically motivated intentional adulteration. Every participant in the supply chain should know and monitor their supply chain for any adulterated materials and take all reasonable precautions to prevent intentional adulteration.[9]

4.7 Importation

Excipients manufactured outside the United States are subject to US FDA and US Customs and Border Protection (CBP) regulations for importation into the United States. The Bioterrorism Act (Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Title III—Protecting Safety and Security of Food and Drug Supply)[10] has further formalized the requirements for importation of foods and drugs into the United States.

Overseas manufacturers of excipients used in drugs, food, and dietary supplements intended for human or veterinary use who intend to export products into the United States are required to follow the FDA, CBP, and Bioterrorism Act regulations. A streamlined process for the importation of excipients used in pharmaceuticals, food, and dietary supplements must be followed and implemented before the imports are allowed into the United States.

The manufacturing facilities and the manufacturers who produce the excipients should be registered with FDA. An FDA registration number is required for importation. In addition, FDA requires information about Prior Notice (PN) of Imports. Upon receipt of the information, FDA grants a PN confirmation number. FDA must confirm PN before the products are shipped, and the PN confirmation number must appear on the customs declaration that accompanies the package. PN information can be submitted electronically to FDA's Prior Notice Systems Interface (PNSI), a free Internet application that allows facilities to provide information regarding the expected imports. PN information also can be submitted via CBP's Automated Commercial System (ACS), a system that processes imports and obtains information needed to make decisions regarding articles entering the United States.

CBP processes imports of all goods for entry into United States, including but not limited to pharmaceuticals, food, and dietary supplements. CBP inspects but does not release products regulated by the FD&C Act and delegates the final release responsibility at the port of entry to the FDA for such materials. After reviewing the PN information, FDA may determine that the regulated articles should not be allowed into the United States or may allow conditional import of articles subject to testing and release at the port of entry. In addition, during FDA review at the port the regulated articles must meet all requirements of the FD&C Act and 21 CFR before they are released by FDA to the importer.

Importers of record (individuals or companies) for excipients can contract with a broker to transmit PN information and other documents for them. In this case, the submitter is the person responsible for providing the information, but the broker is the transmitter. Brokers are licensed private individuals or companies regulated by CBP who aid importers and exporters in moving merchandise through CBP. Brokers provide the proper paperwork and payments to CBP for clients and charge a fee for this service. Before brokers apply for a license, they must pass the customs broker examination.

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[7] FD&C Act. Chapter V: Drugs and Devices. Sec. 501. [21 USC §351] Adulterated Drugs and Devices. http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/FDCActChapterVDrugsandDevices/ucm108055.htm.

[8] FD&C Act. Chapter IV: Food. Sec. 402. [21 USC §342] Adulterated Food. http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/FDCActChapterIVFood/ucm107527.htm (Accessed June 6, 2011).

[9] FDA. Public Meeting on Economically Motivated Adulteration. 2009. http://www.fda.gov/NewsEvents/MeetingsConferencesWorkshops/ucm163619.htm (Accessed June 6, 2011).

[10] FDA. *Guidance for Industry: Questions and Answers Regarding the Interim Final Rule on Prior Notice of Imported Food, (Edition 2); Availability.* 2004. http://www.gpo.gov/fdsys/pkg/FR-2004-05-03/pdf/04-10023.pdf (Accessed June 6, 2011).

FDA currently uses its Operational and Administrative System for Import Support (OASIS)[11] for making its admissibility determinations to ensure the safety, efficacy, and quality of the foreign-origin products for which FDA has regulatory responsibility under the FD&C Act. OASIS is integrated with CBP's ACS and FDA's PNSI systems to receive information related to imported articles.

US Customs and FDA storage areas at the Port of Arrival may not strictly be in compliance with storage conditions required for certain excipients. Importers of record and brokers who represent importers must ensure that the products are released from Customs and FDA inspection as soon as possible. If release is delayed, FDA generally allows removal by Customs and FDA and quarantine in the importer's warehouse until release. FDA staff who review imports at the port of entry are trained to understand that pharmaceutical excipients must be stored under defined conditions. The manufacturer, the importer on record in the importing country, and brokers have a responsibility in working with Customs and FDA staff to ensure that the storage conditions do not adversely affect product quality during quarantine and review.

4.8 Traceability

4.8.1 TRACEABILITY

The pedigree of the excipient should be tracked from the manufacturer's storage through the final delivery to customers by means of recorded identification. The entire supply chain should provide full traceability (for example, via lot numbers and shipping documents) in order to allow fast and efficient investigation of any quality issue or product recall. Every entity in the supply chain should also take responsibility from the preceding supplier and pass the product to subsequent intermediaries down to the end user. Therefore, the original excipient manufacturer and subsequent handlers should always be traceable, and the information should be available both downstream and upstream in the supply chain. All parties to the excipient supply chain should ensure that the excipient is strictly handled according to GDP at every stage.

To ensure the integrity of the supply chain, intermediaries should use contracts, agreements, inspections, and audits downstream and upstream to monitor compliance with GDP principles. When multiple entities constitute the supply chain for each single batch of excipient, each entity should provide its own supplier's certification documentation (see *Appendix: Definitions and Acronyms*) that represents their manufacture or receipt of the excipient batch through release to the subsequent entity. The total of each entity's supplier certification documentation should represent the entire supply chain from original excipient manufacture through use in the final drug product.

4.8.2 TRACEABILITY-RELATED DOCUMENTS

To ensure traceability, all entities in the supply chain should have clear definitions about the shipping documents to be expected with every delivery. At a minimum the documents for every delivery should provide the following information:

- Name and grade of the excipient
- Lot number(s) assigned by the original excipient manufacturer (see *Section 3.4.2 Repackaging and Labeling Batches*)
- Quality and compliance data (e.g., COA) of the excipient
- Origin of the excipient (manufacturer and manufacturing site)
- Original excipient COA(s) (see *Section 3.4.5 Certificates of Analysis*)
- Entity and site of repackaging (when performed), including opening or relabeling the original excipient manufacturer's packaging for any purpose
- Date of shipment and carrier
- Consignor and consignee

A copy of the COA also should accompany the shipment (see ▲*Significant Change for Bulk Pharmaceutical Excipients* ⟨1195⟩ ▲(CN 1-May-2021) and *Bulk Pharmaceutical Excipients—Certificate of Analysis* ⟨1080⟩).

In the event of repackaging from the original excipient manufacturer's package into another container (including any breach or labeling that does not result in a new package), the identity and address of the repackaging entity should be included in the shipping documents.

Additional data resulting from analyses conducted by entities other than the laboratory of the original excipient manufacturer should be provided, along with a clear indication of the source. Quality documents should facilitate traceability back to the original manufacturer with contact information. The COA issued by the manufacturer should indicate which results were obtained by testing the original material and which results were obtained by other means. A distributor should not change the original title and data of the COA or other quality documents. Whenever possible, the original excipient manufacturer's documentation should be used, or data transcription should be verified. The original manufacturing site should be identified on the COA.

If any lot mixing is carried out, COAs from manufacturers are no longer valid, and the distributor should perform analyses in its own laboratory or at an approved and qualified contract laboratory. The distributor should supply a COC, and if the blended lot has not been retested, the distributor should inform the customer that the material is a mixture of different original excipient manufacturers' lots, provided that all other repackaging and storage activities are carried out according to GDP.

SECTION 5: EXCIPIENTS USED IN PHARMACY COMPOUNDING

Although analytical testing of incoming components by the compounding pharmacy to confirm quality attributes stated in the COAs is ideal, generally because of resource limitations, compounding pharmacists rely upon the distributors of excipients for assurance of quality and pedigree. Additional guidance on the quality attributes of excipients received by compounding

[11] FDA. Operational and Administrative System for Import Support (OASIS). 2009.

pharmacies can be found in *USP* general chapter *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩. In certain instances *USP–NF* handles compounded preparations differently than commercially manufactured lots. For example, expiration dates are assigned to commercially manufactured products, and beyond-use dates are assigned to compounded preparations (see *Labeling* ⟨7⟩*, Labels and Labeling for Products and Other Categories, Compounded Preparations*). A similar situation is needed for bulk pharmaceutical excipients as not all excipients that are useful in compounding are listed in official compendia (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩).

State boards of pharmacy regulate pharmacy compounding. USP standards are provided in *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩, *Pharmaceutical Compounding—Sterile Preparations* ⟨797⟩, and *Quality Assurance in Pharmaceutical Compounding* ⟨1163⟩.

APPENDIX: DEFINITIONS AND ACRONYMS

Acceptance Criteria: The specifications and acceptance or rejection limits—such as acceptable quality level or unacceptable quality level with an associated sampling plan—that are necessary for making a decision to accept or reject a lot or batch of raw material, intermediate, packaging material, or excipient.

ACS: Automated Commercial System.

Adulterated Material: A material that fails to conform to its purported quality standard or is intentionally contaminated, diluted, or substituted for another substance or which was not manufactured, processed, packaged, distributed and held in conformance with current good manufacturing practice.

Audit: An assessment of a system or process to determine its compliance with the requirements of a particular standard of operation. See also External Audit, Internal Audit, and Third-Party Audit.

Batch (Lot): A defined quantity of processed excipient which can be expected to be homogeneous. In a continuous process, a batch corresponds to a defined portion of the production based on time or quantity (e.g., vessel's volume, one day's production, etc.).

Batch Number (Lot Number): A unique and distinctive combination of numbers and/or letters from which the complete history of the manufacture, processing, packaging, coding, and distribution of a batch can be determined.

Batch Process: A manufacturing process which produces the excipient from a discrete supply of raw materials processed through discrete unit operations in one mass.

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.

Broker: An entity that acts as an intermediary between a buyer and a seller of products or services. Brokers neither buy nor take possession of the products or services.

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.

CBP: Customs and Border Protection.

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

CFR: Code of Federal Regulations.

CFR (Cost and Freight, Named Destination): (Incoterm) Seller must pay the costs and freight to bring the goods to the port of destination. However, risk is transferred to the buyer once the goods have crossed the ship's rail (maritime transport only).

cGMP: Current good manufacturing practices.

CIF (Cost, Insurance, and Freight, Named Destination): (Incoterm) Same as CFR except that the seller must, in addition, procure and pay for insurance for the buyer.

CIP (Carriage and Insurance Paid, Named Destination): (Incoterm) The containerized transport or multimodal equivalent of CIF. Seller pays for carriage and insurance to the named destination, but risk passes when the goods are handed over to the first carrier.

Closed-Container Distributor (Pass-Through Distributor): A distributor who sells only products that are tested, packaged, and sealed in the containers provided by the original manufacturer.

Closed System: A system that is isolated from its surroundings by a boundary so that no material can be transferred across it.

COA (Certificate of Analysis): A document that reports the results of a test of a representative sample drawn from the batch of material that will be delivered.

COC (Certificate of Conformance): A document that certifies that the supplied goods or service meets the required specifications. Also known as Certificate of Conformity and Certificate of Compliance.

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

Compounding: The preparation, mixing, assembling, altering, packaging, and labeling of a drug, drug-delivery device, or device in accordance with a licensed practitioner's prescription, medication order, or initiative based on the practitioner/patient/pharmacist/compounder relationship in the course of professional practice (defined in *USP* general chapter *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩).

Consignee/Consignor: Person or firm (usually the seller) who delivers a consignment to a carrier for transportation to a consignee (usually the buyer) named in the transportation documents.

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 manufacturing process that continually produces the excipient from a continuous supply of raw material.

Contract Giver: A person or organization letting a contract.

Contract Acceptor: A person or organization accepting the terms of a contract and thereby agreeing to carry out the work or provide the services as specified in the contract.

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.

Critical to Quality: See *Quality, Critical*.

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

Customer: The organization that receives 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.

Distributor: An entity that buys products from a manufacturer, takes possession of those products, and resells them to another party or parties. An essential characteristic of a distributor is the order of these transactions. Distributors buy products (i.e., hold inventory) before making sales.

Drug Master File (DMF): Detailed information about the manufacture of an excipient that is submitted to the US FDA.

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

Drug Substance: Any substance or mixture of substances that is intended for use 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.

Economically Motivated Adulteration: The fraudulent, intentional substitution or addition of a substance in a product for the purpose of increasing the apparent value of the product or reducing the cost of its production for economic gain.

Electronic Signature: A computer data compilation of any symbol or series of symbols, executed, adopted, or authorized by an individual and intended to be the legally binding equivalent of the individual's handwritten signature.

Excipient: Any substance, other than the active pharmaceutical ingredient or drug product, that has been appropriately evaluated for safety and is included in a drug delivery system to aid the processing of the drug delivery system during manufacture; to protect, support, or enhance stability, bioavailability, or patient acceptability; to assist in product identification; or to enhance any other attribute of the overall safety and effectiveness of the drug delivery system during storage or use.

Excipient Pedigree: Includes documentation of suitable excipient good manufacturing practices applied by the excipient manufacturer and suitable good distribution practices. See IPEC *Excipient Pedigree White Paper*.

External Audit: (See also *Audit, Internal*, and *Third-Party Audit*.) An audit carried out typically on behalf of an excipient manufacturer's customer by a person or organization that is not the manufacturer or the customer.

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.

FCA (Free Carrier, Named Place): The seller hands over the goods, cleared for export, into the custody of the first carrier (named by the buyer) at the named place. This term is suitable for all modes of transport, including carriage by air, rail, road, and containerized/multimodal transport (also called *roll on–roll off*).

FDA: Food and Drug Administration.

FD&C Act: Food, Drug, and Cosmetic Act.

FOB (Free on Board, Named Loading Port): The classic maritime trade term according to which the seller must load the goods on board the ship nominated by the buyer, and cost and risk are divided at ship's rail. The seller must clear the goods for export. The purchaser is then responsible for all further costs associated with transport, importation, and storage until the shipment reaches its destination. The term also is applied to air transport when the seller is not able to export the goods according to the time schedule detailed in the letter of credit. In this case the seller allows a deduction equivalent to the carriage by ship from the air carriage. FOB also can be qualified in other ways. For example, *FOB Factory Gate* means that title and responsibility change as soon as the shipment leaves the supplier's premises.

Forwarding Agents (Freight Forwarders): Agents who assist other organizations or individuals in moving cargo to a destination and are familiar with the import and export rules and regulations of their own and foreign countries, the methods of shipping, and the documents related to foreign trade.

Freight Forwarder: See *Forwarding Agent*.

GDP: Good distribution practices.

GMP: Good manufacturing practices.

Headspace: The volume left at the top of an almost-filled container before sealing.

HACCP (Hazard Analysis Critical Control Point): Hazard Analysis and Critical Control Points has seven principles established by the National Advisory Committee for Microbiological Criteria for Foods to control product safety.

Importer: Either the US owner or consignee at the time of entry into the United States or the US agent or representative of the foreign owner or consignee at the time of entry into the United States who is responsible for ensuring that goods offered for entry into the United States are in compliance with all laws affecting the importation.

Impurity: A component of an excipient that is not the intended chemical entity or a concomitant component but is present as a consequence of either the raw materials used or the manufacturing process and is not a foreign substance.

Independent: In the context of internal audits, the quality of being free from any influence, economic or otherwise, from the group, department, or organization under audit.

In-Process Control: Checks performed during production in order to monitor and if necessary to adjust the process to ensure that the material conforms to its specifications. The control of the environment or equipment also can be regarded as a part of in-process control.

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

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

Internal Audit: An audit conducted by an employee of the organization or by an individual from outside the organization, but on behalf of the organization, to determine the effectiveness of a system. (See: *Audit*, *External Audit*, and *Third-Party Audit*).

International Nonproprietary Name: International Nonproprietary Names (INN) facilitate the identification of pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property. A nonproprietary name also is known as a generic name.

ISO: International Organization for Standardization.

Lot: See *Batch*.

Labeling: The affixing to a container or vessel of a tag or document that contains information about that container and its contents.

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.

Nonconforming Material: A material that is deficient in a characteristic, product specification, process parameter, record, or procedure that renders its quality unacceptable, indeterminate, or not according to specified requirements.

OASIS: Operational and Administrative System for Import Support.

Original Excipient Manufacturer: Organization responsible for manufacturing, under appropriate GMPs, the excipient(s) distributed and addressed by this chapter.

Packaging/Repackaging Distributor: A distributor who transfers products from the original packaging or transport vessel(s) provided by the original manufacturer into alternative packaging and sells the products in the alternative packages. See *Distributor* and *Repackager*.

Primary Container–Closure System: The packaging components that come into direct contact with the excipient in the closed, sealed package during storage and transport.

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

Packaging: The container and its components that hold the excipient for storage and transport to the customer.

Pass-Through Distributor: See *Closed-Container Distributor*.

PN: Prior notice.

PNSI: Prior Notice Systems Interface.

Primary, Secondary Packaging: See *Packaging/Repackaging Distributor* and *Primary Container—Closure System*. Packaging materials which do not come into contact with the excipient during the normal course of storage and transport of the excipient.

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

QbD (Quality by Design): A systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control based on sound science and quality risk management. It means designing and developing products and manufacturing processes to ensure a predefined quality.

QMS: Quality management system.

Quality Assurance (QA): The total of the organized arrangements made to ensure that all excipients are of the quality required for their intended use and that quality systems are maintained. See *Quality Unit*.

Quality Control (QC): Checking or testing that specifications are met. See *Quality Unit*.

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.

Quality Management System (QMS): Management system that directs and controls a pharmaceutical company with regard to quality.

Quality Manual: Describes the elements of the QMS and includes the quality organizational structure, written policies, procedures, and processes or references to them, and a description of departmental functions as they relate to the policies, procedures, and processes. Document specifying the quality management system of an organization.

Quality Unit: See also: *Quality Control* and *Quality Assurance*. A group within a larger organization that is responsible for monitoring and ensuring all aspects of quality. Current industry practice generally divides the responsibilities of the quality control unit (QCU), as defined in the cGMP regulations, between quality control (QC) and quality assurance (QA) functions. QC usually involves (1) assessing the suitability of incoming components, containers, closures, labeling, in-process materials, and the finished products; (2) evaluating the performance of the manufacturing process to ensure adherence to proper specifications and limits; and (3) determining the acceptability of each batch for release. QA primarily involves (1) review and approval of all procedures related to production and maintenance, (2) review of associated records, and (3) auditing and performing/evaluating trend analyses.

Quarantine: The status of materials isolated physically or by other effective means pending a decision about 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.

Recall: See *Retrieval*.

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

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

Recommended Re-evaluation Date: The date suggested by the supplier when the material should be re-evaluated to ensure continued compliance with specifications. It differs from the Expiration Date because the excipient can be re-evaluated to extend the length of time the material can be used, if supported by the results of the evaluation and appropriate stability data.

Repackager: A person or organization that takes an excipient from the original manufacturer's container and repackages it into different containers. See also *Distributor* and *Packaging/Repackaging Distributor*.

Repackaging: Removal of the excipient from its original container (combination of secondary and/or primary packaging), and transfer to another container.

Reprocessing: Introduction of previously processed material that did not conform to standards or specifications back into the process and repetition of one or more necessary steps that are part of the normal manufacturing process.

Retrieval (Recall): 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.

Secondary, Primary Packaging: See *Primary, Secondary Packaging*.

Senior Management: See *Top Management*.

Significant Change: A change that alters an excipient's physical or chemical property from the norm or that is likely to alter the excipient's performance in the dosage form.

Specification: The quality parameters to which the excipient, component, or intermediate must conform and that serve as a basis for quality evaluation.

Stability: Continued conformity of the excipient to its specifications.

Stable Process: A process whose output, regardless of the nature of the processing (batch or continuous), can be demonstrated by appropriate means to show a level of variability that consistently meets all aspects of the stated specification (both USP and customer specifications) and thus is acceptable for its intended use.

Subcontractor: A person or organization that undertakes work or services on behalf of a different person or organization that in turn is contracted to undertake work or provide services from the original contract giver.

Supplier's Certification Documentation: Specific information and data associated with a single batch of an excipient. Its accuracy is certified by the business entity that has had control of the same single batch of excipient. Supplier's Certification Documentation includes both quality and supply chain data and information. The methods and processes that derive the included data and information should be understood and controlled, and all data and information sources should be traceable. All entities that take possession and responsibility for the excipient batch should provide Supplier's Certification Documentation including the original excipient manufacturer, all distributors, and all repackagers. Special attention and clarity should be applied within the Supplier's Certification Documentation in any event that breaches the original manufacturer's packaging and/or labels (including addition of new labels).

Third-Party Audit: An audit conducted by an individual from outside the organization and who is neither a supplier nor customer of the organization, e.g., a certification body, to determine the effectiveness of a system.

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 depends on how the quality management system is organized.

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

Trader: An entity that buys products from a manufacturer, may or may not take possession of the products, and resells them to another party or parties. [NOTE—In the case of traders, the sale usually is made before product purchase.]

User: A person or organization that uses pharmaceutical excipients to manufacture pharmaceutical intermediates or finished products.

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.