GOOD MANUFACTURING PRACTICES FOR BULK PHARMACEUTICAL EXCIPIENTS

BACKGROUND

Many of the principles in this general information chapter are derived from an international guidance on the extent and point of application of appropriate good manufacturing practice principles. It is intended to assist excipient manufacturers in determining whether the methods used in, and the facilities and manufacturing controls used for, production adequately ensure that an excipient possesses the quality, purity, safety, and suitability for use that it purports to possess.

The principles and information in this chapter can be applied to the manufacture of all bulk pharmaceutical excipients (referred to throughout this document as "excipient(s)" intended for use in human drugs, veterinary drugs, and biologics. It covers the quality systems and the extent of good manufacturing practices necessary throughout the chain of production up to and including delivery to customers. As an international guidance document, it does not provide information for all national legal requirements nor cover in detail the particular characteristics of every excipient. The quality system standard used as a framework for this chapter is ISO 9002, which is appropriate to manufacturing. Information specific to excipients has been added. Because of the diversity of excipients, some principles in this information chapter may not be applicable to certain products and processes.

This information chapter combines existing governmental regulatory good manufacturing practices principles and international quality system requirements as developed by The International Organization for Standardization (ISO). In view of the increasing globalization of the pharmaceutical industry and the harmonization of pharmaceutical registration requirements, deference to both schemes is becoming necessary. Therefore, relevant portions of both manufacturing concepts are employed throughout this chapter.

The General Guidance section provides an overview of the appropriate manufacturing practices criteria applicable to excipient manufacture and the point of application of excipient good manufacturing practices and quality systems. This section also recommends measures to limit contamination of an excipient and provides the relationship of excipients to finished dosage forms. For a list of terms and their definitions used in this information chapter, see Appendix 1. The section Excipient Quality Systems provides information on the requirements necessary for compliance with relevant good manufacturing practice principles and implementation of an excipient quality system. Information for production facility requirements are included under Process Control. No attempt has been made to include details specific to particular excipients. The information under Appendix 2, General Auditing Considerations, sets forth key criteria to aid in the audit of an excipient manufacturing facility.

GENERAL GUIDANCE

International regulations governing drugs require that components of the drugs be manufactured, processed, packed, and held in accordance with good manufacturing practices. Unlike other pharmaceutical products and components, until now there was no guidance that specifically addressed the manufacture of bulk pharmaceutical excipients.

Excipients are substances, other than the active drug substance or finished dosage form, that have been appropriately evaluated for safety and are included in drug delivery systems 1) to aid in the processing of the drug delivery system during its manufacture; 2) to protect, support, or enhance stability, bioavailability, or patient acceptability; 3) to assist in product identification; or 4) to enhance any other attribute of the overall safety, effectiveness, or delivery of the drug during storage or use.

The application of good manufacturing practices to excipients is relevant when it is determined that a chemical is intended for use as a component of a drug product. Excipient manufacture should be carried out in accordance with the manufacturing practice concepts consistent with the information in this chapter. The objective of excipient good manufacturing practices is to ensure that excipients are manufactured with the appropriate quality characteristics.

Excipients generally are manufactured on a large scale, which means that the use of automated process controls and continuous stream processing are more likely to be utilized. Production equipment and operations will vary depending on the type of excipient being produced, the scale of production, and the type of operation (e.g., lot or batch versus continuous). The use of automated equipment is appropriate when adequate inspection is conducted and calibration and maintenance procedures are followed.

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

ISO 9000 series is a quality system standard of general application that can be applied to every aspect of manufacturing to the benefit of both the manufacturer and customer. It has taken several years since its introduction in 1987 for the ISO 9000 series to be utilized worldwide. There is no current regulatory requirement in Europe, Japan, or the United States for third party certification. A manufacturer may apply the standard with or without certification. However, certification has the benefit of providing assurance to customers that conformance to this quality system has been independently confirmed. Incorporation of GMP requirements into the ISO 9000 quality system enhances not only the quality system, but a company's operational procedures as well. Final dosage formulators worldwide increasingly regard compliance with ISO 9002 as an essential qualification for their suppliers. Obtaining certification is a business decision and is not discussed in this general information chapter.

Excipient Purity

The processes used for the production of bulk pharmaceutical excipients and those used for the production of bulk pharmaceutical chemicals are similar. Both can be manufactured by chemical synthesis, recombinant DNA technology, fermentation, enzymatic reactions, recovery from natural materials, or any combination of these processes. Impurities, contaminants, carriers, vehicles, inert ingredients, diluents, or unwanted crystalline or molecular forms may be present in the raw materials. Therefore, the starting materials for excipients may not be required to be manufactured in accordance with the manufacturing practices specified in this chapter because
often the starting materials (or their derivatives) undergo significant chemical change and physical modification or blending, with the result that many of the impurities present in the starting materials are removed. The ultimate manufacturing objective is purification and physical or chemical alteration, which is accomplished by various chemical, physical, or biological processing steps. The effectiveness of these steps is confirmed by chemical, biological, and physical testing of the excipient. Excipients, once synthesized or isolated, normally undergo additional, extensive purification during manufacture.

Many excipients have applications other than for pharmaceutical uses and are used in food, cosmetics, or industrial products. Thus, environmental conditions, equipment, and operational techniques employed in excipient manufacture often reflect the chemical industry rather than the pharmaceutical industry. Many chemical processes have the potential to produce toxic impurities from side reactions. Therefore, careful process control may be essential. Also, the manufacturing environments may contain deleterious substances. However, chemical processes used to manufacture excipients are either performed in closed systems that afford protection against such contamination—even when the reaction vessels are not enclosed in buildings—or else these processes are in environments that must be controlled.

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

Excipients in Finished Dosage Forms

The formulator of finished dosage forms is highly dependent on the excipient manufacturer to provide bulk pharmaceutical excipients that are uniform in chemical and physical characteristics. This is particularly important in the context of the product approval process where bioequivalency comparisons are made between pivotal clinical biobatch production and commercial scale-up lots or batches. To provide adequate assurance of drug product performance, the excipient used to manufacture commercial lots or batches should not significantly differ from those used in biobatches. Where significant differences do occur, additional testing by the manufacturer of finished dosage forms may be required to establish the bioequivalence of the finished product. It remains equally important to ensure that the bioequivalence of subsequent, post-approval commercial lots or batches of drug product is not adversely affected over time.

In general, excipients are used as purchased. Consequently, impurities present in the excipient will be present in the finished dosage form. While manufacturers of dosage forms may have limited control over excipient quality through specifications, the excipient manufacturer has greater control over physical characteristics, quality, and the presence of impurities in the excipient.

Excipients are used in different types of dosage forms where physical characteristics, such as particle size, may be important. While it is primarily the responsibility of the manufacturer of finished dosage forms to identify the particular physical characteristics needed, it is the responsibility of the excipient manufacturer to adequately control processes to ensure the excipient's consistent conformance to specifications. The excipient's end use should be identified and considered during inspection of excipient manufacturers' facilities.

Particularly important is whether the excipient is a direct component of a drug dosage form, whether the excipient will be used in the preparation of a sterile dosage form, or whether the excipient is represented as pyrogen free. The excipient manufacturer is responsible for ensuring that excipients are pyrogen free if the manufacturer makes such a representation in specifications, labeling, contractual agreement, or a Drug Master File (DMF).

EXCIPIENT QUALITY SYSTEMS

The information described below can be used as the basis for a quality system in the manufacture of excipients. Procedures that are utilized in the manufacture and control of excipients should be written. Conformance to those procedures should be documented. A quality manual is a documented base and is intended to describe the quality policy and the commitment of the supplier to quality. The procedural system should have adequate formal controls related to procedure approval, revision, and distribution. These controls should provide assurance that the proper version of a procedure is being utilized throughout the operation.

Management and Employee Responsibility

Quality Policy—Management should demonstrate commitment to a quality policy that should be implemented within the operational unit. Management should participate in the development of the company's quality policy and provide the resources necessary for development, maintenance, and review of such policy and quality system at least annually. Management should be committed to this policy and should appoint appropriate company personnel to be responsible for coordination and implementation of the quality system.

Organization—There should be a quality unit, independent of production, that has the responsibility and authority to approve or reject all components, in-process materials, packaging materials, and finished excipients. The quality unit should have the authority to review production records to ensure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality unit should be responsible for approving or rejecting excipients manufactured, processed, packaged, or held under contract by another company. The quality unit can delegate these responsibilities if proper controls, such as periodic audits and documentation of training, are in place. Adequate laboratory facilities for the testing and approval or rejection of raw materials, packaging materials, in-process materials, and finished excipients should be available to the quality control unit.

It is the responsibility of an independent unit, usually the quality assurance group, which is independent of production, to participate in issuing procedures, authorizing changes to processes, specifications, procedures, and test methods and in investigating failure and complaints.

An organization chart by function should be available showing interdepartmental relationships as well as relationships to the management of the company. As a minimum, all quality assurance, quality control, production maintenance, and engineering functions should have clear job descriptions.

Personnel—

Employee Responsibility—Employees engaged in the manufacture, processing, packaging, or holding of an excipient should wear clean clothing appropriate for the duties they perform. Protective apparel, such as head, face, hand, and arm coverings, should be worn as necessary to protect excipients from contamination. Only employees authorized by supervisory personnel should enter those areas of the buildings and facilities designated as limited-access areas.

Employees should practice good sanitation and health habits. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions that may adversely affect the safety or quality of excipients should be excluded from direct contact with components, excipient containers and closures, in-process materials, and finished excipients until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of the excipients. All employees should be instructed to report to supervisory personnel any health conditions that may have an adverse effect on excipients.

Other Requirements—There should be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packaging, or holding of each excipient in a manner consistent with the information in this guide. Management should establish adequate and continued good manufacturing practices and personal hygiene training for all employees handling products so that they understand the precautions necessary to prevent the contamination of excipients.
Consultants—Consultants advising on the manufacture, processing, packaging, or holding of excipients should have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained. Records should be maintained listing the name, address, and qualifications of any consultants and the type of service they provide.

Technical Assistance—The excipient manufacturer should establish and maintain procedures for providing such technical assistance as may be required.

Manufacter and User Responsibilities

Contract Review—The manufacturer and user should mutually agree upon the excipient specifications. The manufacturer must have the facility and process capability to consistently meet the mutually agreed upon specifications of the excipient(s). Subcontracting or significant changes to a supplier's audited process that could affect the physical, chemical, or functionality of the excipient in a final dosage form should be immediately communicated or pre-approved as mutually agreed upon between customer and supplier.

Document and Data Control—The excipient manufacturer should have a system to control all documents and data that relate to the requirements of the quality system. When these documents were issued and where they are located should be recorded. To identify the most recent document, each document should include a unique identifier, date of issue, and revision number on each page. The issuing department also should be identified. All changes, where practical, and the reasons for the change should be documented. Documents and subsequent changes to the documents should be reviewed and approved by designated qualified personnel before issuance to the appropriate areas identified in the documents.

Purchasing—The purchaser should verify that the supplier of raw materials, components, and services for the manufacture of excipients has the capability to consistently meet the agreed-upon requirements. This may include periodic audits of the vendor's plant, if deemed necessary. Purchasing agreements should contain data clearly describing the product ordered, including where applicable, the following:

- The name, type, class, style, grade, item code number, or other precise identification traceable to the raw material specification.
- Drawings, process requirements, inspection instructions, and other relevant technical data, including requirements for approval or qualification of product, procedures, process equipment, and personnel.

These requirements also apply to selection and control of subcontractors. Subcontractors include toll manufacturers and contract laboratories.

Control of Customer Supplied Products—The manufacturer should establish and maintain procedures for verification, storage, and maintenance of customer supplied products intended for incorporation into the customer's excipients. Verification by the manufacturer does not relieve the customer of the responsibility to provide an acceptable product. Any product that is lost, damaged, or is otherwise unsuitable for use should be recorded and reported to the customer. In this case, procedures should be in place for acceptable disposition and replacement of the product.

Product Identification and Traceability—All items, from the received raw materials, through the in-process goods, to the finished products, should be clearly identified and traceable through a documented system. The system should allow the traceability of product upstream and downstream. Identification of raw materials used in the production of processed materials should be traceable using a batch numbering system or any other appropriate system. The finished product should be traceable to the customer and retrievable in case of the need for a product recall.

Labeling—Labeling requirements for excipient packages are subject to applicable national and international regulatory requirements, which may include transportation and safety measures. Procedures should be employed to protect the quality and purity of the excipient when it is packaged, and to ensure that the correct label is applied to all containers. A good system of labeling should have, at a minimum, the following features: the name of product; the manufacturer and distributor; a lot or batch number from which the complete lot or batch history can be determined; a file of master labels [note—A designated individual should review incoming labels or labels printed on demand against the appropriate master labels]; storage of labels in separate containers or compartments to prevent mix-ups; formal issuance of labels by requisition or other document; issuance of an exact number of labels, sufficient for the number of containers to be labeled, retention copies, and calculated excesses, if any; reconciliation of the number of labels issued with the number of unit packaging and retention labels, together with the destruction of excess labels bearing lot or batch numbers; and avoidance of labeling more than one lot or batch at a time without adequate separation and controls.

In instances where excipients are labeled on the packaging line, packaged in pre-printed bags, or bulk shipped in tank cars, there should be documentation of the system used to satisfy the intent of the above requirements.

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

Retained Samples—Reserve samples of an excipient should be retained for one year after the expiration or re-evaluation date, or for one year after distribution is complete, whichever is longer. Sample size should be twice the amount required to perform specification testing.

Process Control

Buildings and Facilities—Any building or buildings used in the manufacture, processing, packaging, or holding of an excipient should be of suitable size, construction, and location to facilitate cleaning, maintenance, and proper operations.

Cross-contamination Prevention—Cross-contamination should be a consideration in the design of the manufacturing process and facility. The minimization of the degree of cross-contamination should be dependent on the safety and intended use of the excipient.

It is expected that the degree of precautions taken in minimizing cross-contamination be appropriate to the conditions of the manufacturing facility. Where two different grades of the same excipient are manufactured in the same building or the same equipment, a trace carryover from the production of the previously produced grade to the present production may occur. This can be considered acceptable if shown that the extent of comingling does not change the functionality and safety of the excipient.

When the excipient product is initially recovered, it should be in a clean environment and not exposed to airborne contaminants such as dust, other excipients, or industrial chemicals. The primary consideration is that the building and facilities be designed so that operations performed within do not contribute to an actual or potential contamination of the excipient.

Air Handling—Excipient plant air handling systems should be designed to prevent cross-contamination. For dedicated areas processing the same excipient, it is permissible to recycle a portion of the exhaust air back into the same area. The adequacy of such a system of operation for multi-use areas, especially if several products are processed simultaneously, should be carefully analyzed.

In multi-use areas where several products are completely confined in closed vessels and piping systems, the extent of filtration of the supply air (combined fresh make-up air and recycled air) is acceptable if the conditions are consistent with other existing regulations (e.g., environmental, safety). However, there should be data to demonstrate adequacy of the air handling system. Where for process reasons an inert gas is needed, these same rules should apply.
Cleaning and Sanitary Conditions— Adequate cleanliness is an important consideration in the design of excipient manufacturing facilities. Any building used in the manufacture, processing, packaging, or holding of an excipient should be maintained in an appropriately clean and sanitary condition. There should be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials used in cleaning the buildings and facilities; such written procedures should be followed and periodically reviewed. Conformance should be documented.

All buildings should be free of infestation by rodents, birds, insects, and other vermin. Waste should be held and disposed of in a timely and appropriate manner. However, many starting materials, particularly botanicals, may have some unavoidable contamination, such as rodent or other animal filth or infestation. The manufacturer should have sufficient control methods to prevent the increase of such contamination or infestation in holding areas or its spread to other areas of the plant.

Other Facility Concerns— Any building used in the manufacture, processing, packaging, or holding of an excipient should be maintained in a good state of repair. The following items are of particular concern:

[PLUMBING]— Water that comes in contact with an excipient should be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to the excipient. Drains should be of adequate size and, where connected directly to a sewer, should be provided with an air break, or other mechanical device, to prevent back-siphoning.

[WASHING AND TOILET FACILITIES]— Adequate washing facilities should be provided, including hot and cold water, soap or detergent, air dryers or single service towels, and clean toilet facilities easily accessible to working areas.

Equipment— Equipment used in the manufacture, processing, packaging, or holding of an excipient should be of appropriate design, adequate size, and in a suitable location to facilitate its operation, cleaning, and maintenance.

Outside Equipment— Some fermentation tanks, reaction vessels, and certain other equipment may not be situated within a building, and a considerable amount of processing may occur out-of-doors. Such processing is acceptable provided it occurs in a closed system.

Multipurpose Equipment— Many excipients are produced using multipurpose equipment. With few exceptions, such multiple usage is satisfactory provided the equipment can be adequately cleaned according to validated written procedures. The program should take into consideration the need for different cleaning procedures, depending on the safety considerations of the product or intermediate and what product or intermediate was previously produced. Products that leave residues that cannot be easily removed should be produced in dedicated equipment.

Where multipurpose equipment is in use, it is important to be able to determine previous usage when investigating cross-contamination or the possibility of such contamination. An equipment cleaning and use log, while desirable and perhaps preferable, is not the only method of determining prior use. Any documentation system that clearly identifies the previous lot or batch and shows that the equipment was cleaned is acceptable.

Cleaning and disinfection procedures should be properly established by competent personnel using the model product approach, when applicable. These procedures should be designed to meet or exceed the particular needs of the product and process involved and be set down in a written schedule available for the guidance of employees and management. An effective and regular cleaning program should be put in place to remove product residues and dirt, which may also contain microorganisms and act as a source of contamination.

The supplier should demonstrate the effectiveness and efficiency of the cleaning and disinfection procedures for each piece of equipment, and the cleaning status of equipment should be recorded. Validation data should prove that the cleaning procedure is acceptable. An evaluation should consider the potential impact that traces of contaminant may have on the product supplied to the customer. All equipment that has been in contact with contaminated material should be thoroughly cleaned and disinfected before coming in contact with an excipient.

Controlled Environment— A controlled environment may be necessary to avoid microbial contamination or degradation caused by exposure to heat, air, or light. The degree of protection required may vary depending on the stage of the process. Equipment should be designed to minimize the possibility of contamination caused by direct operator contact in such activities as the unloading of centrifuge bags, use of transfer hoses (particularly those used to transfer powders), and the operation of drying equipment and pumps. The sanitary design of transfer and processing equipment should be evaluated. Those with moving parts should be assessed in regard to the integrity of seals and packing materials to avoid their contaminating the product.

Special environments required by some processes should be monitored at all times to ensure product quality (e.g., inert atmosphere, protection from light). Where inert atmosphere is required, the gas should be treated as a raw material. If interruptions in a special environment occur, adequate evidence and appropriate rationales should be documented to show that such interruptions have not compromised the quality of the excipient. Such environmental concerns become increasingly important after purification of the excipient has been completed.

Construction— Process equipment should be constructed so that their contact surfaces will not be reactive, additive, or absorptive so as to alter the quality attributes of the excipient. Substances required for operation, such as lubricants or coolants, should not come into contact with components, excipient containers, closures, in-process materials, or finished excipients. Materials acceptable for food grade use should be used where product exposure or contamination is possible.

Maintenance— Equipment and utensils should be maintained and sanitized (where necessary) at appropriate intervals to prevent malfunctions or contamination that would alter the standards and characteristics of the excipient beyond the official, or otherwise established, requirements. Written procedures should be established and followed for maintenance of critical equipment, including utensils, used in the manufacture, processing, packaging, or holding of the excipient. Records should be kept of preventive maintenance of equipment and utensils, a description of the maintenance performed, and the batch or lot number of the excipient that was present in the equipment before and after the activity.

These records can be in the form of a log, computer database, or other appropriate documentation, provided the system can properly identify who was responsible for performing each function.

Water Systems and Water Quality— Potable water may be used in the production of excipients, provided that established water quality standards are consistent with regulatory requirements for source drinking water. If the manufacturer specifies water of pharmacopeial quality in the specifications or DMF, the water should meet the particular pharmacopeial standards. Data from periodic testing should be available to show compliance with chemical and microbiological standards, including freedom from pathogenic organisms. Data need not be generated by the manufacturer if such data are available from municipal water authorities.

While drinking water is used for many excipient processes, Purified Water is also widely used in the manufacture of excipients. Because of the well-recognized potential for microbial growth in deionizers and ultrafiltration or reverse osmosis systems used to produce Purified Water, such systems should be properly validated and controlled.

Proper control methods include the establishment of water quality specifications and corresponding action levels, remedial action when microbial levels are exceeded, and
adequate maintenance procedures such as regeneration and sanitation or sterilization.

Appropriate specifications for chemical and microbial quality should be established and periodic testing conducted. Such specifications will vary depending on the process and the point in the process when the water is used. The water quality standards should reflect the intended use of the excipient. The frequency of microbial and chemical testing of Purified Water is dependent upon a variety of factors, including the test results and the point in the process (e.g., final wash in centrifuge) at which such water is used.

Similar principles to those discussed above for Purified Water apply to Water For Injection used in sterile and pyrogen-free excipient processing. The water for injection (WFI) system should be monitored for microorganisms, and the validation data and reports of monitoring should be reviewed as is required for finished dosage forms.

Most purified and WFI water systems, including ultrafiltration and reverse osmosis systems, have the potential for the development of endotoxins. If the final excipient product purports to be pyrogen free or sterile, or will be used in preparing parenteral products, validation of the system to control endotoxins should be conducted and routine testing of the process water for endotoxins should be performed (preferably by the LAL method).

Aseptic and Sterile Manufacturing—The manufacture of sterile excipients for use in aseptic or sterile processing presents technical challenges. Because humans are the primary source of contamination in an aseptic operation, the process should be designed to eliminate this direct contact. Those aseptic excipient operations that utilize considerable operator involvement should have adequate controls.

The excipient manufacturer should document the sanitizing of critical processing equipment. Processes used for the sterilization of equipment should be validated. The manufacturer also should verify that no chemical interaction with the product occurs.

There are guidelines and compliance programs that provide detailed guidance for the manufacture of sterile products. These documents should be reviewed in association with the sterile excipient manufacturing inspections.

Validation of Process and Control Procedures—Excipient manufacturers are expected to adequately determine and document that all significant processing steps are performed consistently. The type of excipient, the breadth of the specification relative to the degree of process control, and other factors determine the extent of the process development and documentation required.

An important factor in the assurance of product quality includes the adequate design and control of the manufacturing process because product testing alone is not sufficient to reveal variations that may have occurred. Each step of the manufacturing process should be controlled, to the extent necessary, to ensure that the excipient meets established specifications. The concept of process validation is a key element in assuring that these quality assurance goals are met. Documentation describing the process reactions, operating parameters, purifications, impurities, and key tests needed for process control should be written, thus providing the basis for validation.

Many manufacturers already possess the data necessary to validate that their processes perform in a consistent manner. For example, limitations of a reaction or purification step are usually identified in the development phase. Known impurities and tests used to determine their levels are also established at this phase. Thus, when the process is scaled up to production of a lot or batch size, a comparison can be made with development lots or batches. Scale-up and development reports, along with purity profiles, would constitute an appropriate validation report.

Stability—While many excipient products are very stable and may not require extensive testing to ensure stability, the stability of excipients is an important contributing factor to the stability of the finished dosage form. The stability of excipients may be affected by undetected changes in raw material specifications or subtle changes in manufacturing procedures. Excipient products also may be shipped in a large variety of different packaging types that can affect their stability (e.g., drums that are metal and plastic, bags and bottles that are plastic or glass, tank cars, etc.).

Some excipients may be available in different grades (i.e., various molecular weights of a polymer or different monomer ratios, etc.) or may be mixtures or blends of other excipients. These excipients may be very similar to others within a product group. Minor quantitative differences of some of the components may be the only significant variation from one product to another. For these types of excipients, a model product approach may be appropriate to assess the stability of similar excipients. Stability studies would involve the selection of several model products that would be expected to simulate the stability of the product group being assessed. This election should be based on scientifically sound theories. Data from stability studies of these model products can be used to determine theoretical stability for similar products.

There should be a documented testing program designed to assess the stability characteristics of excipients. The results of such stability testing should be used in determining appropriate storage conditions and their re-evaluation or expiration dates. The testing program should be ongoing and should include the following: the number of lots per year, sample size, and test intervals; the storage conditions for samples retained for testing; those test methods that are necessary to indicate stability; and a simulation of containers and storage time equivalent to those conditions in the marketplace, if possible.

For excipients that have been in the market for a long time, historical data may be used to assign the shelf life and storage conditions. The testing program can also be modified based on available historical data.

Expiration Dating and Re-evaluation—If testing indicates a short shelf life under anticipated storage conditions, the excipient should either be labeled with an expiration date or be re-evaluated at appropriate intervals to determine its continued suitability for use. If the excipient has been in the market for a long time, the expiration date or its re-evaluation must be derived from appropriate stability testing or from historical data. With few exceptions, expiration dates are not presently considered to be a general requirement for all excipients. Thus, the absence of an expiration date is not objectionable.

Process Changes (Change Control)—The excipient manufacturer should establish and maintain written procedures for the identification, documentation, appropriate review, and approval of changes within the production processes. An independent group (such as regulatory affairs, quality assurance, etc.) should have the responsibility and authority for the management and final approval of changes. Significant operational changes should be based on validated excipient studies. The effect of the changes should be communicated to both internal and external customers.

Lot or Batch Production Records—There is increased use of computer systems to initiate, monitor, adjust, and otherwise control manufacturing processes. These operations may be accompanied by recording charts that show key parameters (e.g., temperature) at suitable intervals, or even continuously throughout the process. In other cases, key measurements (e.g., pH) may be momentarily displayed on a monitor screen but not available in hard copy. In both cases, conventional hard-copy lot or batch production records such as those showing the addition of ingredients, actual performance of operations by identifiable individuals, and other information usually seen in conventional records may not be generated. Therefore, documentation of the excipient manufacturing process should include a written description of the process and production records.

As a practical matter, when computers and other sophisticated equipment are employed, the following considerations are essential: systems and procedures that show the equipment and software is in fact performing as intended; checking and calibrating the equipment at appropriate intervals; retention of suitable backup systems, such as copies of the program and files; and assurance that changes in the program are documented, validated, and made only by authorized personnel.
documented. In order to ensure batch uniformity, homogeneous mixing of all materials, to the extent feasible, and reproducibility from batch to batch is essential. Blending of batches or lots that individually do not conform to specifications with other lots that do conform (to salvage or hide adulterated material) is not an acceptable practice.

In-process blending or mixing, which is performed to facilitate processing, includes the use of holding tanks, reprocessing, and repeated crystallizations. Incidental carryover is another type of in-process mixing that frequently occurs and is usually acceptable because cleanup between successive lots or batches of the same excipient is not normally required to maintain quality levels during a production operation.

Solvents, Mother Liquors, and Second Crops—Many excipients are extracted from, or purified by, the use of organic solvents. These solvents are normally removed by drying the moist excipient. It is important that excipient specifications include tests and limits for residues of solvents.

Solvents may be recovered and reused in the same process or different processes provided that the recovered solvents are shown to meet appropriate standards prior to reuse or commingling with other approved material. Mother liquors or filtrates containing recoverable amounts of excipients, reactants, or intermediates are frequently reused. Recovery procedures for such excipients are acceptable if the recovered excipient meets its specifications and recovery procedures are indicated in lot or batch production records. Recovery procedures for reactants and intermediates are acceptable if the recovered materials meet suitable specifications.

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

Finished Product Testing and Release—Finished product testing should be performed by the quality unit and should conform to written specification. There should be a procedure that ensures that appropriate manufacturing documentation, in addition to the test data, is evaluated prior to release.

All appropriate records relating to inspection and testing should be available for review. Where the process is continuously monitored, acknowledgment that the process was monitored and the results of the monitoring should be available.

Control of Nonconforming Product—Any raw material, intermediate, or finished excipient found not to meet specifications should be clearly identified and segregated to prevent inadvertent use or release for sale. A record of nonconforming product should be maintained. All incidence of nonconformance should be investigated to identify the root cause. This investigation should be documented and corrections made to prevent recurrence of the problem.

Procedures should exist for the evaluation and fate of nonconforming products. Nonconforming product should be reviewed in accordance with documented procedures to determine its final outcome. The nonconforming product may be reprocessed or reworked to meet the specified requirements and then accepted with agreement by the customer, regraded for alternative applications, or destroyed.

Returned Excipient Products—Returned excipient products should be identified as such and held. If the conditions under which the products have been held, stored, or shipped before and during return, or if the condition of the container casts doubt about its safety, identity, strength, quality, or purity, the product should be destroyed unless examination, testing, or other investigations prove that the excipients meet appropriate standards of safety, quality, or purity.

Records of returned products should include the name and lot number (or control batch number), reason for the return, quantity returned, date of disposition, and ultimate fate of these products. Procedures for the holding, testing, and reprocessing should be written and followed.

Corrective and Preventive Actions—The supplier should establish, document, and maintain procedures for

- investigating the cause of nonconforming product, returns, and complaints along with the corrective action needed to prevent recurrence;
- analyzing all processes, work operations, concessions, quality records, and service reports to detect and eliminate potential causes of nonconforming product;
• initiating preventive actions to deal with problems at a level corresponding to the risks encountered;
• applying controls to ensure that corrective actions are taken and that they are effective; and
• implementing and recording changes in procedures resulting from corrective action.

Reprocessing or Reworking— Reprocessed or reworked product should be re-inspected in accordance with documented procedures. Reprocessing or reworking of an excipient may be acceptable. However, merely relying on final testing of the reprocessed excipient as a means of demonstrating compliance to specification and neglecting the investigation and evaluation of the manufacturing process is unacceptable.

Reprocessed material should also be evaluated and documented to ensure that the lot or batch will conform with all established standards, specifications, and characteristics equivalent to those of the original material. There should be a sufficient investigation, evaluation, and documentation to show that the reprocessed excipient is at least equivalent to other acceptable products and that the nonconformance did not result from an inadequate process. If the need for reprocessing resulted from human error, it may indicate other deficiencies, such as inadequate training or work instructions.

Reprocessing or rework that is not a normal part of the validated process should not be performed without the review and approval of an independent group such as regulatory affairs, quality assurance, etc.

Inspection, Measuring, and Test Equipment

Calibration of all in-process instruments identified as quality instruments, as well as test equipment used in the laboratory, should be traceable to recognized standards. Laboratory instruments, such as spectrometers, viscosimeters, and other apparatus, as well as reagents, buffer solutions, and standard solutions would be included.

The control program should include the standardization or calibration of reagents, instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy or precision limits are not met. Reagents, instruments, apparatus, gauges, and recording devices not meeting established specifications should not be used.

Computer systems used to verify that the product conforms to specifications should be audited to ensure satisfactory performance.

Handling, Storage, Preservation, Packaging, and Delivery

Handling, Storage, and Preservation— Excipient products, intermediates, and raw materials should be handled and stored under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity are not affected. Storage and handling procedures should protect containers and closures from contamination and deterioration and should prevent mix-ups (e.g., between containers that have different specifications but are similar in appearance).

Raw materials, including solvents, are sometimes stored in silos or other large containers, making precise separation of lots or batches difficult. If such materials are used, this should be noted in an inventory or other record, with reasonable accuracy.

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

Packaging System— An excipient packaging system should include, at a minimum, the following features:

• Written specifications, examination or testing methods, and cleaning procedures where so indicated.
• Tamper evident seals, particularly if the excipient claims to be sterile or nonpyrogenic or if returned material is to be restocked.
• Evaluation of the container closure system, in which it is demonstrated that there is adequate protection from deterioration and contamination and that the excipient is not altered beyond its established specifications.
• All previous labeling removed or defaced if returnable excipient containers are reused. If the containers are repetitively used solely for the same excipient, all previous lot or batch numbers or the entire label should be removed or completely obliterated.

Delivery— The manufacturer should arrange for the protection of the quality of product after final inspection and test. Where contractually specified, this protection should be extended to include delivery to the destination.

Distribution records should be kept that document all shipments of finished products. To facilitate its recall, if necessary, these records should identify by excipient batch or lot where and to whom the product was shipped, the amount shipped, the carrier, and the date of shipment.

Quality Record Control

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

All quality records should be legible and identify the product involved. Quality records should be kept for at least as long as samples are retained or in accordance with legislative requirements. These records should be stored in facilities that provide a suitable environment to minimize deterioration or damage and to prevent loss and should be maintained in such a way that they are readily retrievable.

Batch production and control records should be prepared for each batch of excipient produced and should include complete information relating to the production and control of each batch. These records should include an accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed; and documentation that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished, including the following:
• Dates
• Identity of individual major equipment and lines used, and specific identification of each batch of component or in-process material used
• Weights and measures of components used in the course of processing
• In-process and laboratory control results
• Inspection of the packaging and labeling area before and after use
• A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing
Complete labeling control records, including specimens or copies of all labeling used

Description of drug product containers and closures

Any sampling performed

Identification of the persons performing and directly supervising or checking each significant step in the operation

Any investigation made for failures and discrepancies

Results of examinations made during final product inspection.

Internal Quality Audits

The excipient manufacturer should carry out a comprehensive system of planned and documented internal quality audits to verify whether quality activities comply with planned arrangements and to determine the effectiveness of the quality system. Audits should be scheduled on the basis of the status and importance of the activity. The audits and follow-up actions should be carried out in accordance with documented procedures.

The results of the audits should be documented and brought to the attention of the management personnel having responsibility in the area audited. The management personnel responsible for the area should take corrective action on the deficiencies found by the audit.

Training

The excipient manufacturer should establish and maintain procedures for identifying and providing the training needs of all personnel performing activities affecting quality. Appropriate records of training should be maintained. Training should directly relate to the employee's function or performance of specific operations and to good manufacturing practices. This training should be conducted by qualified individuals on a continuing basis and with sufficient frequency to ensure that employees remain familiar with any applicable manufacturing practice requirements.

APPENDIX 1. DEFINITIONS

Active Ingredient: a substance or bulk pharmaceutical chemical that is 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 man or other animals.

Adulterated Substance: a material that has either been contaminated with a foreign substance or not manufactured using good manufacturing practices. This definition does not pertain to materials that do not meet physical or chemical specifications.

Aseptic: an environment free from pathogenic microorganisms.

Batch (Lot): a defined quantity of raw material, intermediate material, packaging components, or final product processed so that it is 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 volume, one day's production, etc.).

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

Batch Numbering System: a standard operating procedure (SOP) describing the details of assigning batch numbers.

Batch Record: documentation that provides the history of a batch from the raw material stage to completion of the batch or lot.

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

Certificate of Analysis: a document relating specifically to the results of testing a representative sample drawn from the material to be delivered.

Clean Area: an area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants in the area.

Commingling: the blending of trace carryover material from one grade of an excipient with another, usually due to a continuous process.

Contaminant: an impurity not intended to be present in an excipient, which may be introduced by poor cleaning, processing, or lack of appropriate environmental and personnel controls during the manufacturing process.

Continuous Process: a manufacturing process that continually produces an excipient from a continuous supply of raw materials.

Critical Process: a manufacturing process step that may cause variation in quality attributes.

Cross-contamination: contamination during production of a raw material, intermediate, or of a finished excipient with another raw material, intermediate, or product.

DMF: detailed information submitted to the United States Food and Drug Administration concerning a specific facility, process, or product intended for incorporation by reference into a new drug application, supplemental new drug application, abbreviated new drug application, or investigational new drug application.

Excipient: any substances, other than the active drug or product, that have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing of the drug delivery system during its manufacture, protect, support or enhance stability, bioavailability, or patient acceptability, assist in product identification, or enhance any other attribute of the overall safety and effectiveness of the drug delivery system during storage or use.

Expiration Date: the date beyond which the product may no longer conform to relevant specifications.

Finished Dosage Form (Drug Product): a finished pharmaceutical product, prepared for consumer applications, containing excipients and the active drug substance.

Finished Product: any pharmaceutical product that has undergone all stages of production, including packaging and labeling.

Finished Process Product: a product that has undergone all stages of production and is released from quality control.

Homogeneous Material: throughout the batch, material of uniform consistency and composition.

Impurity: a substance contained in a product other than the desired substance.

In-Process Testing: monitoring checks performed during production to ensure that the product conforms to its specifications.

Identification of the persons performing and directly supervising or checking each significant step in the operation

Any investigation made for failures and discrepancies

Results of examinations made during final product inspection.

Internal Quality Audits

The excipient manufacturer should carry out a comprehensive system of planned and documented internal quality audits to verify whether quality activities comply with planned arrangements and to determine the effectiveness of the quality system. Audits should be scheduled on the basis of the status and importance of the activity. The audits and follow-up actions should be carried out in accordance with documented procedures.

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Certificate of Analysis: a document relating specifically to the results of testing a representative sample drawn from the material to be delivered.

Clean Area: an area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants in the area.

Commingling: the blending of trace carryover material from one grade of an excipient with another, usually due to a continuous process.

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Continuous Process: a manufacturing process that continually produces an excipient from a continuous supply of raw materials.

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Cross-contamination: contamination during production of a raw material, intermediate, or of a finished excipient with another raw material, intermediate, or product.

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Excipient: any substances, other than the active drug or product, that have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing of the drug delivery system during its manufacture, protect, support or enhance stability, bioavailability, or patient acceptability, assist in product identification, or enhance any other attribute of the overall safety and effectiveness of the drug delivery system during storage or use.

Expiration Date: the date beyond which the product may no longer conform to relevant specifications.

FinishedDosage Form (Drug Product): a finished pharmaceutical product, prepared for consumer applications, containing excipients and the active drug substance.

Finished Product: any pharmaceutical product that has undergone all stages of production, including packaging and labeling.

Finished Process Product: a product that has undergone all stages of production and is released from quality control.

Homogeneous Material: throughout the batch, material of uniform consistency and composition.

Impurity: a substance contained in a product other than the desired substance.
In-Process Material: any material that must undergo further manufacture before it becomes a bulk product.

Intermediate Product: any material that must undergo further manufacturing steps before it becomes a bulk product.

Lot: See Batch.

Manufacturer: the company that performs the final production steps and release of the product.

Manufacturing Process: all steps necessary to produce a finished product from raw materials.

Master Formula (Master Formula Record): documentation describing the manufacture of the excipient from raw material to completion of the lot or batch.

Material Review Board: a committee or group selected to evaluate the disposition of potentially nonconforming material.

Model Product: a product that simulates a group of like products.

Mother Liquor: a concentrated solution from which the product is obtained by evaporation, freezing, or crystallization.

Re-evaluation Date: that date beyond which the bulk pharmaceutical excipient should not be used without prior adequate re-examination.

Representative Sample: a sample drawn according to an appropriate sampling plan, which may involve regular or random selection.

Reprocessing: introducing back into the process previously processed material that did not conform to standards or specifications and repeating steps that are already part of the normal manufacturing process.

Nonconforming Material: any material that does not meet manufacturer's specifications or applicable good manufacturing practices.

Packaging: the act of filling and labeling a container with a product.

Packaging Material: the containers, closures, and labels employed in the packaging of a product.

Processing Instructions: the manufacturing procedures set forth in the master formula.

Production: all operations involved in the preparation of an excipient pharmaceutical product, from receipt of raw materials through the completion of a finished product.

Purification: the process of removing impurities from a substance.

Quality: the totality of features and characteristics of a product that bear on its ability to satisfy stated or implied needs.

Quality Assurance: all those planned and systematic actions necessary to provide confidence that a product or a service will satisfy given requirements for quality.

Quality Control: all activities such as measuring, examining, testing, or gauging one or more characteristics of a product (including raw materials) and comparing the findings with specified requirements to determine conformance.

Quality Control Instruments: measurement instruments used to monitor the manufacturing process, in-process controls, and the finished excipient products for final quality control approval.

Quarantine: the status of any material isolated physically or by other effective means while awaiting a decision on its use.

Raw Material: any substance used in the production of a product excluding packaging materials.

Reserve (Retained) Sample: a representative sample of the final excipient batch of sufficient quality and quantity necessary to perform quality control analyses twice.

Returned Products: finished products sent back to the manufacturer.

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

Significant Processing Step: processing steps that are required to produce an excipient that meets the established physical and chemical criteria.

Shelf Life: the length of time during which the excipient exhibits stability.

Specifications: the quality parameters that serve as a basis for quality evaluation and to which the products or materials must conform.

Stability: the continued conformance of the excipient to its specifications.

Standard Operating Procedures (SOPs): a written authorized procedure that gives instructions for performing operations.

Validation: documentation that states that any procedure, process, equipment, material, or activity consistently leads to the expected results.

Vendor: an organization contracted to supply a material or perform a service.

APPENDIX 2. GENERAL AUDITING CONSIDERATIONS

Evaluation

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

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

Other factors that should be considered in evaluating an excipient plant are the degree of exposure of the material to adverse environmental conditions, the potential for cross-contamination from any source, the relative ease and thoroughness of clean-up, and sterile versus nonsterile operations.
Documentation—An excipient manufacturer should recognize the need for appropriate evaluation and utilization of proper standards and test procedures for raw materials before they are introduced into the process. In addition, as chemical processing proceeds, a chain of documentation should be established that includes the following:

- A written process
- Identification of critical processing steps
- Appropriate production records
- Records of initial and subsequent lot or batch numbers
- Records of raw materials used
- Intermediate test results with meaningful standards.

The production of some excipients involves processes in which chemical and biochemical mechanisms have not been fully characterized; therefore, the methods and procedures used in their production will often differ from those applicable to the manufacture of finished dosage forms.

It should be recognized that all intermediates need not require testing. An excipient manufacturer should, however, be able to identify critical or key points in the process where selective intermediate sampling and testing is necessary in order to monitor process performance. The records should become more complete as the end of the process approaches. The finishing steps and packaging steps should be conducted under appropriate conditions to avoid contamination and mix-ups and be appropriately documented.

Inspections

Inspection of an excipient operation may depend on the purpose of the audit and intended use of the excipient. Operational limitations and validation of the significant processing steps of a production process should be examined to determine that the manufacturer adequately controls steps to ensure that the process performs consistently. Overall, an inspection should determine the excipient manufacturer's capability to deliver a product that consistently meets the specifications listed in the marketed application or the product specifications needed for research purposes. A team consisting of auditors, engineers, laboratory analysts, purchasing agents, computer experts, or other appropriate personnel should participate in the inspection when resources permit. Confidentiality of the manufacturers' processes must be respected by external auditors.

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

- Nonconformance—This could be because of the rejection of a lot or batch that did not meet specifications, customer complaints, return of a product by a customer, or recall of a product. The cause of the nonconformance should have been determined by the manufacturer, a report of the investigation prepared, and subsequent corrective action initiated and documented. Records and documents should be reviewed to ensure that nonconformances are not the result of a poorly developed or inconsistent process.
- Complaint files—Customers may report some aspects of product attributes that are not entirely suitable for their use. These may be caused by impurities or inconsistencies in the excipient manufacturing process.
- Change control logs
- Material Review Board documents or equivalent team reports
- Master formula and lot or batch production records—Frequent revisions may reveal problems in the excipient production process.
- Specifications for the presence of unreacted intermediates and solvent residues in the finished excipient
- Storage areas for rejected products.

Significant Processing Steps

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

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

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

Documentation and Record Keeping

Documentation required for the early steps in the process should provide a chain of documentation, but need not be as comprehensive as in latter parts of the process. The minimum documentation that should be applied in order to promote uniformity in excipient GMP inspections is:

- the assignment of a unique lot or batch number to the released or certified excipient
- the preparation of a lot or batch record
• demonstration that the lot or batch has been prepared using GMP guidelines from the processing point at which excipient manufacturing practices have been determined to apply

• demonstration that the lot or batch is homogeneous within the manufacturer's specifications (This does not necessitate final blending of continuous process material if process controls can demonstrate compliance to specifications throughout the lot or batch.)

• demonstration that the lot or batch is not commingled with material from other lots or batches for the purpose of either hiding or diluting an adulterated batch

• demonstration that the lot or batch has been sampled in accordance with a sampling plan that ensures a representative sample of the lot or batch

• demonstration that the lot or batch has been analyzed using scientifically established tests and methods designed to ensure that the product meets standards, specifications, and characteristics

• demonstration that an excipient has stability data to support the intended period of use. (These data can be obtained from actual studies on the specific excipient or from applicable model product studies that can reasonably be expected to simulate the performance of the specific excipient.)

Complete documentation should exist when:

• the excipient can be identified and quantified for those processes where the molecule is produced during the course of the process (In this regard, a theoretical yield should be established with appropriate limits, and there should be an investigation if the actual yield falls outside the limits.)

• a contaminant, impurity, or other substance likely to adversely affect the purity or form of the molecule is identified and subsequent attempts are made to remove it

• any significant aberration occurs outside of the normal manufacturing process.

Complete documentation should be continued throughout the remainder of the process for all significant processing steps until the excipient is packaged and transported to the end user.

Product Lot or Batch Consistency and Audit

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

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

A review of a process flow chart is helpful in understanding the various processing stages. As part of the review of the processing records, the critical stages and sampling points should be identified. The normal limits from in-process testing should be determined, along with the action to be taken by the manufacturer should these specifications not be met. For example, an in-process test result may show the presence of some unreacted material which may indicate that the process time should be extended.

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