

## Auditing an Excipient Supplier

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# Audit Training Manual: 21

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important and excipient suppliers need to adhere to relevant GMPs.

Excipients are used to aid the safety, effectiveness or delivery of the dosage form. This may include assisting in the processing of the drug delivery system; or, enhancing stability, bioavailability, or patient acceptability.

### Example of common excipients:

- Fillers:
  - lactose
  - calcium phosphates
  - starch
  - mannitol
  - microcrystalline cellulose
- Binders
  - hydroxypropylmethyl cellulose
  - starch paste
  - polyvinylpyrrolidone
- Colorants
  - dyes
  - lakes (Al oxides)
- Disintegrants
  - croscarmellose sodium
  - crospovidone
  - sodium starch glycolate
- Surfactants
  - sodium lauryl sulfate
- Lubricants
  - magnesium stearate
  - stearic acid
  - hydrogenated vegetable oil
- Glidants
  - colloidal silica

### Excipient Manufacturing

Many excipient materials are also used in industries other than the pharmaceutical industry, including food, cosmetic or industrial products. In many cases excipients are foodstuffs, food additives, or food preservatives that are also used in pharmaceutical products. Most pharmaceutical excipient manufacture is less than 10 percent of the production of the material. In most cases, the material is produced in bulk and is a low margin product.

Excipient manufacturing processes are often similar to those for chemical APIs. Excipients are often manufactured on a large scale utilizing continuous processing and automated process controls. Facilities may consist of large tanks; production facilities and equipment will vary depending upon the type of excipient being manufactured, the scale of production and the type of operations (batch processing vs continuous processing). In some cases the manufacturing plant and processes used to produce excipients may be the same as those used to produce food, cosmetic or industrial products with additional controls applied only at the isolation, packing, quality control testing and/or warehousing.

### **Why audit an excipient manufacturer?**

Most excipients are used as purchased from the manufacturer. Most GMP sites depend on the manufacturer to provide product that is uniform in chemical and physical characteristics and that meets established site specifications. Even though GMP site can establish specifications for the excipient, only the manufacturer can completely control the physical characteristics, the quality and the presence of impurities.

The objective of an excipient GMP audit is ensuring that the manufacture results in the uniform characteristics and quality, and the desired specifications.

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- phase separation (e.g., filtration, centrifugation)
- chemical form changes (hydration, acetylation or formation of a salt)
- weighing or volumetric measurements that are required to be precise
- physical changes (milling, blending)
- final steps (purification, packaging, coating)

**Consideration should be given to the appropriate controls for the quality critical steps and risks to final product for excipients produced sterile or pyrogen free, and for all excipients used in the formulation of parenteral or inhalation pharmaceutical dosage forms.**

### Key GMP Principles to consider during an audit

#### A. Control of impurities and contamination

Usually the customer does not perform further chemical processing or purification on excipients, and the material is used as purchased. If an impurity is present in the excipient it will probably be present in the finished drug product.

The manufacturing environment should be evaluated. External contamination can arise from the manufacturing environment when the product is exposed if adequate controls are not in place. In excipient manufacture, chemical processes are often performed in closed systems that offer protection against environmental contamination.

Consider the following factors:

- Closed or open systems (evaluate charging and emptying from reactors)
- Multi-use of reactors (are the same reactors used for different reactions or multipurpose, or dedicated reactors)
- Form of the material (wet vs dry)
- Criticality of the processing stage
- Continuous vs batch processing
- Potential for cross contamination

The potential risk in terms of raw materials, lubricants and manufacturing process in regards to Transmissible Spongiform Encephalopathies and compliance to current legislative guidance such as ‘Committee for Proprietary Medicinal Products (CPMP) – Note for Guidance on Minimising Risk of Transmitting Animal Spongiform Encephalopathies via Human and Veterinary Products’ should be evaluated.

<http://www.emea.eu.int/pdfs/vet/regaffair/041001en.pdf>

Other considerations of potential raw material contamination impacts, e.g. Avian Flu, should be evaluated during the audit.

#### B. Change control

Since the excipient is used without further processing, GMP site requires consistent excipient quality – both chemical and physical parameters. It is the responsibility of the excipient manufacturer to control excipient manufacturing processes to ensure consistent conformance to excipient specifications.

Changes in excipient manufacturing processes may result in changes of physical or chemical properties that only become evident in the finished dosage form. This is important to a GMP site from a finished dosage form manufacturability as well as from the

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significant process, testing method, specification and facility changes prior to implementation and 2.) how this change will affect the excipient being produced. Verify that the Quality Control Unit's authority and responsibilities are clearly defined in writing.

- Verify that an internal quality audit program for all areas of operation has been established to verify that SOP's and other procedures and policies are being followed, and to determine the effectiveness of the quality systems.
  - Verify that approved procedures exist for processing and investigating complaints, as well as reporting complaints and tracking resolutions.
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- Ensure that there is adequate documentation
    - Verify that there are written SOP's for all areas of operation.
    - Verify that procedures are in place for the identification, collection, indexing, filing, storage, maintenance and disposition of controlled documents.
    - Verify that there are procedures in place to insure retention of the records for every batch for at least one year past expiration or re-evaluation date (if one is assigned), or one year after distribution is complete (whichever is longer).
  
  - Ensure that there are sufficient qualified personnel and resources. Personnel should have the appropriate combination of education, training and experience for their assigned job.
    - Verify that there is a documented training and qualification program for each job classification.
    - Verify that job-specific training is conducted and documented for each employee.
    - Verify that training is conducted with sufficient frequency to assure that employees remain familiar with applicable regulations.
    - Verify that there are clearly written job descriptions for all personnel.
    - Verify that the training program incorporates requirements for temporary employees and consultants.
    - Verify that personnel wear appropriate clothing and practice good sanitation habits.
  
  - Determine that the supplier has a controlled system for management of materials.
    - Verify that there is a list maintained of approved sources for raw materials used in the manufacturing process.
    - Verify that there is an adequate communication system to assure that suppliers and subcontractors notify the company of significant changes.
    - Verify that there is a system in place to trace raw materials back to their original suppliers.
    - Determine any risks associated with animal spongiform encephalopathies and other potential contamination considerations (e.g. Avian Flu).
    - Verify that batch/lot numbers for finished product are unique and provide traceability of the batch throughout the manufacturing process.
    - Verify that there are adequate written and approved instructions for raw material sampling and testing.
    - Verify that appropriate controls are exercised to assure raw materials are approved prior to being used in production, and that access to quarantined material is restricted.

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- Verify that the process water meets suitable standards; potable water standards at minimum.
- Verify adequate lighting is provided.
- Verify that in areas where excipient is open to the environment, drains are of adequate size and, where directly connected to a sewer, have an air break or other device to prevent back-siphoning.
- Verify adequate personal washing facilities are provided.
- Ensure that the process is controlled.
  - Verify that the supplier's SOPs for cleaning and change over from one product to another have enough detail. Verify that there is adequate documentation to support the effectiveness of these procedures.
  - Ensure that there is an adequate system for documenting cleaning.
  - Determine if there are cleaning procedures for cleaning different excipient grades.
  - Verify that there is evidence that the cleaning process for non-dedicated equipment is adequate to remove previously manufactured material.
  - Verify that the product contact surfaces of all processing equipment are not reactive, additive, or absorptive and will not adversely affect the product.
  - Determine if there are any other grades of the excipient.
  - Determine if there are any other products manufactured at the site (industrial and/or toxic compounds). If there are either industrial or toxic compounds, ensure that there are containment measures and/or procedures in place to prevent contamination of excipient.
  - Verify that there is a system to identify the status of all raw materials, intermediates and finished products. All containers and equipment should be clearly labeled to identify the contents and, if appropriate, the stage of manufacture.
  - Verify that there are complete written manufacturing instructions/batch reports that specify quantity and identity of raw materials, equipment, manufacturing flow, operating parameters, in-process sampling, packaging materials, labeling, and documentation of each significant step.
  - Verify that there is evidence to demonstrate that the manufacturing process produces finished product that meets established specifications consistently from batch to batch.
  - Verify that critical process parameters have been defined.
  - Verify that there is an adequate system, described in a SOP, for controlling process changes. The system should include 1.) maintenance of a change log, 2.) involvement by the quality unit in the change procedure, and 3.) evaluation of the impact of the change on the excipient.
  - Verify that there are procedures in place for investigating and determining the disposition of in-process materials, intermediates or finished excipients that do not meet specifications. **Non-conforming finished excipient lots should not be blended with conforming lots.** Procedures should be in place to prevent the blending of nonconforming **finished excipient** batches with conforming batches.
  - Verify that if reprocessing (repeating steps that are already part of the normal process) is performed, there are complete written instructions including any additional testing/inspection that may be required.
  - Verify that if reworking (performing steps that are not part of the normal

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- that does not meet specifications.
  - Verify that nonconforming product is clearly identified and segregated to prevent use or distribution, and that access to this material is restricted.
  - Ensure that investigation records include notification information and are maintained
  - Verify that there is a procedure for assigning expiration and/or recommended re-evaluation dates, supported by sufficient stability data.
  - Verify that there is an SOP for investigating returned goods, including proper identification, segregated storage, testing, and Quality Control involvement in the evaluation and determination of product disposition.
- Ensure the Quality laboratory meets GMPs standards.
    - Verify that training and qualifications are documented for all laboratory personnel.
    - Verify that written and approved test methods and acceptance specifications are available to the analyst for all samples to be tested.
    - Verify that there are procedures for qualification (IQ/OQ) of new and/or modified laboratory instruments and equipment.
    - Verify that there are established practices to insure proper storage and handling of reference standards, reagents, volumetric and test solutions, with labeling to indicate their identity, date of preparation or receipt, expiration date and other appropriate information.
    - Verify that there are procedures for the preparation and maintenance of complete and appropriate written laboratory records.
    - Verify that there are procedures in place for a review of laboratory records by a second chemist, supervisor and/or the Quality Control Unit.
    - Verify that there is a SOP for investigation of out-of-specification (OOS) results, atypical results, and test deviations, including specific procedures for re-measurement or retesting, and a time frame for completing investigations.
    - Verify that the excipient stability has been evaluated and that the results used in determining appropriate storage and expiry or retest dates.
    - Verify that each batch is tested against the appropriate standard and skip testing is not used.
    - Verify that tests are performed in accordance with relevant pharmacopoeias as appropriate.
  - Verify that the Certificate of Analysis (COA) for the excipient includes the following:
    - Name (compendial/trade), grade, pharmacopeial designations, and specific lot/batch number for the material
    - Name of supplier, identity of the manufacturer, and manufacturing site
    - All tests, results, and specifications for the material
    - Date of manufacture
    - Expiration date and/or recommended re-evaluation date
    - Appropriate authorization (signature, title, date)
    - Verify that there is a procedure to insure that **all** information on the final COA receives appropriate review, and that adequate controls are in place to prevent unauthorized changes to the COA.