

Auditing an Excipient Supplier

Goals

When you have completed this unit, you should be able to:

- Perform an audit of an excipient vendor
- Use a range of tools and information, including the contents of this unit and the Internet, in support of auditing an excipient vendor
- Understand and apply applicable GMP standards and site standards to an audit of an excipient vendor
- Recognize compliance or non-compliance of excipient vendors to applicable regulations

Definitions

Excipient: Any material that is used in the manufacture of a Formulated Product that excludes the active ingredient; an excipient may be used during processing but not be present in the final formulation, e.g. Water.

International Pharmaceutical Excipients Council (IPEC): an international industry association formed in 1991 by manufacturers and end-users of excipients. The association includes the United States (IPEC-Americas), Europe (IPEC Europe) and Japan (JPEC). For information, see www.ipec.org.

Pharmaceutical Quality Group (PQG): Pharmaceutical quality and GMP group that publishes codes of practice, standards, and monographs on various aspects of regulatory requirements. For information, see www.pqg.org.

Pyrogen free: free of fever producing substances.

Reprocessing: taking the same material and repeating steps that are already part of the normal process.

Reworking: taking already manufactured material and performing steps that are not part of the normal process.

Regrading of lot: lots manufactured for a pharmaceutical application but used as another grade, usually lower (less pure), due to failure to conform to pharmaceutical specifications.

Certification of Analysis / Certificate of Conformance: : A document issued for a batch of product or ingredient, which certifies that the batch complies with a specified quality specification.

Explanation of Topic

What is an excipient?

An excipient is an additive material used to formulate Active Pharmaceutical Ingredients (API's) into pharmaceutical dosage forms suitable for administration to patients. Excipients are part of the final formulation of a drug product; therefore their quality and stability are

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for the appropriate step in the process for GMP to begin being applied. From that point on, appropriate GMP should be applied. As the manufacturing process progresses from early manufacturing to purification and packaging the stringency of GMP application should increase.

Physical processing such as granulation, milling and blending should be conducted to GMP standards. The criticality of the process step should also be considered to determine the level of GMP control required.

Audits of an excipient manufacturer should take into account the intended use of the excipient and should focus on the quality-critical processing steps that are necessary to produce an excipient that meets criteria.

The manufacturer should identify and have adequate control over these quality critical steps to ensure a consistent process. Quality-critical steps may include:

- phase changes (e.g., dissolution, crystallization, evaporation, drying, sublimation, distillation or absorption)
- 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) –

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- Determine if the processing equipment is dedicated to one product or used for multiple products.
- Determine if equipment is closed, and where product may be exposed to the environment.
- Determine if processing is continuous or batch.
- Verify that there is adequate space and environmental controls to insure product integrity and to prevent cross-contamination or product mix-ups.
- Verify that the manufacturing environments (all production areas) are appropriately controlled for the process taking place to protect the excipient against deterioration and contamination.
- Verify that there is an adequate program to protect components from contamination from insects, rodents, birds and other vermin.
- Verify that there are adequate ventilation systems where product is exposed. Ensure that the air handling system is designed and controlled to prevent cross-contamination.

- 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.