Goals

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

- Perform an audit of an API manufacturer
- Use a range of tools and information, including the contents of this module and the Internet, in support of auditing an API module
- Understand and apply applicable GMP standards to an audit of an API manufacturer
- Recognize compliance or non-compliance of API manufacturers to applicable regulations

Definitions

Active Pharmaceutical Ingredient (API): Any substance or mixture of substances intended to be used in the manufacture of a drug medicinal product and that, when used in the production of a drug, becomes an active ingredient of the drug product.

Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

API starting material: A raw material, intermediate, or an API that is used in the production of an API, which is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a materials purchased from one or more suppliers under contract of commercial agreements, or produced in-house.

API packaging material: Any material intended for protect an intermediate or API during storage and transport.

Batch Production record: The document used for each individual batch of API, based on the master production instruction.

Blending: The process of combining materials, each within the same specification, to produce a homogeneous intermediate or API.

Centrifugation: A method of separating a solid/liquid mixture by rotating it at high speed in a cylindrical container. The solid will remain on the sides (through centrifugal force) while the liquid goes to drain.

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

Critical Process Parameters: A process step, process condition, or any other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification. The requirements or specifications of an API or API process that can be measured and controlled to produce the desired quality of the API.

Critical Quality Attributes: A characteristic of the API that contributes to its quality and

chemical reactions in API manufacturing include Grignard reactions (addition of a reagent to a keton or aldehyde to form a secondary or tertiary alcohol), hydrolysis, halogenation, hydrogenation and oxidations. Frequently, a catalyst is added to the raw materials to initiate a chemical reaction. The catalyst will not be consumed during the chemical reaction. Multiple chemical reactions typically occur to form the "raw" API active molecule. This molecule is not pure and must undergo purification to eliminate process impurities, which may include unreacted raw materials, residual solvents, degradation products, by-products, etc.

The purification may include:

- Distillation
- Extraction
- Filtration

The final molecule is usually in liquid form and has to be isolated through crystallization. Crystallization may be achieved by cooling the reaction mixture or adding a solvent, which causes solid crystals to form within the liquid. This results in a mixture called a slurry. Often, the crystallization may be induced by a seed material. The seed material's role is to induce the desired crystal form of the API. A centrifuge filter pad is used to separate crystals, also known as a "cake" of crystals, from the liquid and then discharge the mother liquor. A mother liquor may contain unreacted materials, intermediates, levels of the API and/or impurities

Recovery (e.g. from the mother liquor or filtrates) of reactants, intermediates, of the API is considered acceptable, provided that approved procedures exist for the recovery. The recovered materials must meet specifications suitable for their intended use.

Once the API has undergone one or more of the above steps, centrifugation or pressure filter may be used to separate the solid (API) from the solvent (fluid). The isolation of the API solid is followed by a drying process. Depending on the finished API particle size requirement and the finished dosage formulation process, a milling step may be required. The regulatory authorities considered milling as part of the pharmaceutical manufacturing process in many countries, particularly if the particle size is of importance in the finished dosage form. The finished API is then packaged and transferred for manufacturing of a finished dosage form.

Important elements of the Quality System

GMP for API manufacturing contains most elements found also in the GMP for finished product dosage forms. Some elements may differ and there are also additional elements to be aware of. Below some of the GMP elements are mentioned briefly and references are made to other training.

It should be noted that for API for use in clinical trials not all GMP controls for manufacturing are appropriate during the development of the new API. Specific guidance is given in section 19 of ICH Q7A.

Quality Management

To ensure that the product meets quality specifications, the API manufacturer must have an established quality unit.

The responsibilities of the Quality Unit cannot be delegated. They include releasing or rejecting

- All APIs,

Critical Quality Attributes (CQA) may include:

- Chemical purity
- Impurity profiles
- Particle size
- Density
- Moisture and solvent content
- Homogeneity
- Microbial quality

Critical Process Parameters that affect Critical Quality Attributes must also be identified and ranges established. Different API processes may have different critical process parameters.

Typical Critical Process Parameters are:

- pH
- Pressure
- Temperature
- Mixing speed

These critical process parameters should be routinely recorded with specified ranges during the manufacturing stages and verified as acceptable at batch release.

Time limits for the completion of significant manufacturing steps should be established and documented. For intermediates that are isolated and stored before further processing, storage conditions, hold times and container types must be specified.

For APIs process changes assurance should be gained that there is no impact upon the impurity profile and/or other key API quality attributes.

Packaging and Labeling should be performed according to written procedures. Printing devices should be monitored to ensure that all imprinting conforms to established specifications.

Where intermediates and APIs are intended to be transferred outside the control of the manufacturer's material management system, retest/expiration dates must be on the label.

The label should contain special shipping or storage conditions for an API or intermediate.

Packaging and labeling facilities should be inspected prior to use, as a precaution for mislabeling. This should be documented. APIs shipped outside of the manufacturer's control must have tamper evident seals attached/securing the container. A system must exist to ensure that the distribution of each lot can be determined in order to facilitate recall procedures.

Storage and Distribution

If agents, brokers, traders, distributors, repackers or relabellers are used it needs to be ensured that they comply with GMP as described in Q7A including maintaining traceability.

produces APIs that meets established specifications consistently from batch to batch.
- Verify that critical process parameters have been defined and are controlled.
- Verify that there is an adequate system, described in an 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
  3) evaluation of the impact of the change on the API.
- Determine if the changes have been performed according to the manufacturing site's change control procedure.
- Confirm that critical process parameters are established and controlled.
- Confirm that process parameters are appropriately documented in batch records.

- Ensure that Packaging and Labelling operations have sufficient control.
  - Protect quality and purity of the API
  - Assurance that the correct label is applied to all containers.
  - Designed to prevent mix-ups.
  - Procedures to ensure that the correct quantity of labels are printed and issued and the labels contain the correct information. Excess labels should be immediately destroyed or returned to controlled storage. All excess labels bearing lot numbers should be destroyed. Packaging and labelling facilities should be inspected immediately before use to ensure that all materials that are not required for the next packaging have been removed. Direct printing should satisfy that intent.

- Review an example of a rework procedure
  - Ensure that a change request was completed for the rework procedure
  - Ensure that the procedure outlined in the change request was followed and documented.
  - Verify that the rework procedure is being concurrently validated.
  - Verify that a regulatory filing was submitted for the rework procedure.

- Review an example of documentation related to reprocessing of material
  - Ensure that the manufacturing steps used match the validated process steps.
  - Ensure that the Critical Process Parameters were met.
  - Ensure that the appropriate release tests have been completed.

- Determine that the API manufacturer has a controlled system for management of materials.
  - Verify that raw materials, including those received in tank trucks, are checked upon receiving to assure that the:
    - Material has the correct labels & compliant C of A/C of C
    - The seal is intact
    - The container is not damaged
  - Verify that there are adequate written and approved instructions for raw material sampling and testing.
  - Verify that raw materials have been assigned a retest date.
  - Verify that the storage of material is designed to prevent contamination, cross contamination and damage.

- Review documentation.
  - Review deviations/investigations and corrective and preventative actions.
    - Ensure that root causes have been identified.