

Auditing an Oral Solid Solution Area

Goals of this Training Unit

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

- Apply the regulatory requirements related to oral dosage forms.
- Perform an audit of oral dosage forms.
- Use a range of information tools, from the contents of this unit to the Intranet in support of an audit of oral dosage forms.
- Recognize compliance or non-compliance of regulations pertaining to requirements for oral dosage forms.

Definitions

Binder: a chemical that acts to hold granules in a tablet together.

Blender discharge: the processed material that is removed from the blender after the processing operation has been completed.

Critical Process Parameter(s): (CCP) a process step, process condition, or any other relevant parameter or item that must be controlled within predetermined criteria to ensure that the product meets its specification. The requirements or specifications of a product that can be measured and controlled to produce the desired quality of the product.

Dry Granulation: modification of the powder morphology using dry compaction forces.

Granulation: the process of creating granules.

Granule: a particle that has been mixed or blended to achieve a certain size, shape and composition. The act or process of forming or crystallizing into grains; as, the granulation of powder and sugar.

Oral solid: a dosage form taken by mouth that may include tablets, gelatin capsules, chewable tablets, or a form of sustained release delivery.

Oral solutions: a liquid dosage form taken by mouth containing an active drug product that is given to a patient. It may be a solution, elixir, or a suspension.

Particle size profile: the percentages of different sized particles that make up a passing granulation process

Wet granulation: adding a liquid to a powder that causes particles to bind together through capillary forces.

Explanation of Topic

What is an oral dosage form?

An oral dosage form may be either a liquid or a solid. Each form uses different manufacturing processes and equipment. This is important to an auditor because some items that are critical in one operation may not be critical to another.

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temperature at which the solvent should be maintained, the mixing speed and time, the holding time and in process assurance of dissolution, are among the critical process parameters.

For oral solutions, the temperature of both the solution and environment should be controlled to prevent microbial growth and loss of potency. The air should also be controlled and monitored. Liquids may be particularly susceptible to microbial and other contamination. Therefore special measures must be taken to prevent any contamination.

For oral suspensions it is of utmost importance to ensure that the liquid doesn't segregate. Appropriate controls should be put in place to ensure homogeneity of batches filled.

Review data that support storage times and transfer operations. There should be established procedures and time limits for such operations to address the potential for segregation or setting as well as other unexpected effects that may be caused by extended holding or stirring.

Oral solutions/suspensions are common for clinical trial material.

Oral solution/suspension dose manufacturing process

Equipment used for batching and mixing of oral solutions and suspensions is relatively basic. Generally, these products are formulated on a weight basis with the batching tank on load cells. The design of the batching tank with regard to the location of the bottom discharge valve may present problems. Ideally, the bottom discharge valve is on level with the bottom of the tank.

Transfer lines are generally hard piped and easily cleaned and sanitized. In some cases manufacturers use flexible hoses to transfer products. Such hoses should be labeled, cleaned and stored in a manner that protects from contamination.

A key aspect in process validation for solutions/suspensions should be to assure that the drug substance and preservatives (if used) are dissolved. Parameters such as heat and time should be measured. Assessment of in-process assay results of the bulk solution during and/or after compounding according to predetermined limits, are also important aspects of process validation. Review the firm's development data/documentation for their justification of the process.

What should be audited?

An oral solid or oral solution/suspension audit should include an examination of the all of the six GMP Systems:

- | | |
|-----------------|--------------------------|
| ➤ Quality | ➤ Facility and Equipment |
| ➤ QA Laboratory | ➤ Material Handling |
| ➤ Production | ➤ Packaging and Labeling |

This training module **will not include** detailed information about the Packaging and Labeling system and the Laboratory system for oral dose products. In-process control laboratories are often different from other laboratories and part of the production area and in-process controls may be performed by operators. As an auditor you need to cover these laboratories as including training of the staff.

The audit of the quality system should include a documentation review of deviations, annual product reviews/product quality reviews, change control, product release, documentation management, training/personnel, and consumer complaints in conjunction with the execution of the audit as outlined for oral solids and solutions. The

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instruments should result in an investigation. Measuring, weighing, recording and control equipment should be of the appropriate range and precision for the intended operation. Controls should be established to assure the integrity of the punches and dies used in compressing tablets.

All equipment and containers used to manufacture a drug should be labeled at all times. The label should identify the contents of the container or equipment including the batch number and the stage of processing. If the equipment is "in use" the tags and charts associated with the equipment should indicate the product number, product name and strength and batch number. For reusable equipment/containers, previous labels must be removed or defaced. If reusable filters are part of the equipment ensure they are product specific if needed. Equipment used during the manufacture of a batch should be identified in the batch record.

Equipment and utensils must be cleaned at appropriate intervals to prevent contamination and malfunction. Time limits for cleaning of production equipment after use must be established and followed. There should also be requirements established for re-cleaning of processing equipment after a specific period of disuse.

In different parts of the world certain products, e.g. hormones, may need to be considered differently from a cross-contamination risk. As an auditor you need to review the policy of the company to ensure that handling of potent products has been considered and is handled appropriately to site requirements.

Equipment and containers not in use should be tagged ("clean", "to be cleaned/dirty" or equivalent wording). Clean tote bins, drums, Glen bowls, fluid beds and other clean equipment should be covered at all times when not in use to minimize potential contamination.

Additionally, requirements should be in place for proper equipment use and maintenance, as well as the performance of failure investigation(s), implementation of corrective and preventative plans, and measures to be taken to recover in the event of a system failure. For example, the option for manual re-inspection processes should a mechanical system fail.

Material handling

Raw materials should be weighed in a separate area to prevent cross contamination. To prevent cross contamination, air pressure differentials should assure that materials do not migrate outside of weighing area. The air pressure differentials should be documented. Daily balance checks should be performed on balances used to weigh raw and in-process materials. Pay attention to cleaning procedures between products.

Components and product containers

Written procedures describing how components, drug product containers, and closures are received, identified, stored, handled, sampled, tested, and approved or rejected must be adhered to and available for review. If the handling and storage of components is computer controlled, the program must be validated. Receiving records must provide traceability to the component manufacturer and supplier. In addition, these records should also include the receiving date, manufacturer's lot number, quantity received, and control number (unique number assigned by the receiving area). The component container should also be identified by this unique identification code (component container units used in the packaging of the batch and documented within the batch record). This unique code provides traceability from the component manufacturer to its

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- Verify equipment identified in the batch record against field equipment is the same, noting calibration and maintenance status.
- Determine if equipment is used for manufacturing more than one product.
- Determine that equipment is cleaned thoroughly by reviewing the equipment use, maintenance and cleaning log.
- Determine how cleaning is documented.
- Ensure that critical equipment is qualified according to the facility's established IQ/OQ procedure.
- Ensure that sterilization and cleaning has been validated.
- Review calibration status of balances.

- Materials Receiving Area
 - Ensure that approved procedures are in place for inspection, sampling, testing and release of incoming materials (raw materials, packaging components, excipients, etc).
 - Confirm, through observation, that procedures are being followed.
 - Determine if raw materials, intermediate products, or final products require special storage conditions or handling procedures.
 - If special storage is needed, confirm that controls are in place to ensure these conditions are met throughout the holding, manufacturing, packaging, and distribution process.
 - Review calibration status of balances in the weighing area.

- Utility systems
 - Determine what type of water is used in the process and in equipment cleaning.
 - Determine if any compressed gases or other utilities are used in the manufacturing process.
 - Ensure that if any utilities contact the product they have been qualified.
 - Ensure that if filters are used in the process they have been qualified or validated according to the established approved facility procedures.
 - Verify that there are air pressure differentials between corridors to process rooms as described in an approved facility SOP and that they are documented.
 - Ensure that there are dust filters in place within the air system and that they are regularly maintained and recorded on a preventative maintenance schedule.
 - Vacuum system

- In the oral solid manufacturing area, observe various process steps and confirm that critical operating parameters are in place, monitored and documented.
 - Verify that weighing, blending/mixing, granulation, tableting/encapsulation, and coating operations are in compliance.
 - Determine documentation items to be reviewed based on observations.
 - Request SOPs and documentation from Facility escort as observations warrant during the walk through.
 - Review manufacturing procedures, such as blending parameters and tableting rates or speed, granulating parameters, holding times (granulation storage, tablet storage, film coating solution storage), and development data to support a manufacturing process change.
 - Observe the addition of drug substance and powder components to manufacturing vessels to determine if operations generate dust.

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