

Auditing an Oral Solid Solution Area

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Solid dosage form

Solid dosage forms may be:

- tablets
- gelatin capsules also known as gel caps
- capsules
- granules

Most solid dose forms usually contain five different types of ingredients. The first, the active pharmaceutical ingredient (API), delivers the therapeutic effect. The second chemical, a binder, is added to the batch to hold the solid (tablet/capsule) together. A disintegrator is added to help the body break down the tablet after administration. A base, which is an inert substance, may be added to provide size and weight to the tablet. It must be compatible with the active pharmaceutical ingredient and not interfere with the therapeutic action of the active pharmaceutical ingredient. One other ingredient that is normally added is a food grade lubricant that prevents the tablet from being caught or stuck in the tableting press. An optional chemical that may be added is either a dye to give color to the tablet and/or a flavoring.

Equipment and processes used for the various manufacturing tasks should be assessed for validation/qualification and calibration status. Dedicated equipment is preferred, however not required. Either way appropriate measures should be in place for labeling, cleaning and storage, as well as in-use practices to protect the equipment, and ultimately the finished drug product from contamination.

Solid dose manufacturing process

Steps in the manufacturing process for most solid dose products are dispensing (weighing) ingredients, blending/mixing ingredients, dry granulation or wet granulation and drying, compressing/tableting, and in some cases, film-coating and/or tablet printing.

Blending/mixing is a process that mixes dry chemicals together to achieve a uniform mix. To use an analogy, if you bake a cake, this is the same as mixing the dry ingredients together. Examples of some equipment used are ribbon blenders, planetary blenders, or diffusion mixers.

The next step is granulation. Granulation uses the dry mixture from the previous step and converts it into larger particles (granules). Granulation is the modification of the powder through the addition of either a liquid (wet granulation), which causes particles to bind through capillary forces, or dry compaction (dry granulation), which forces the powder into uniform size granules. By making uniform size granules, these will then flow more easily into tableting equipment. Equipment used may be a high shear mixer granulator. Typically, the liquid used for wet granulation is a solvent or water. The material, be it solvent or water, should be of suitable quality.

When a wet granulation step is audited, you should check batch records carefully against critical process parameters, which include rate and amount of solvent used, and length of granulation time. Following wet granulation, the granulated product is dried in temperature-controlled dryers. There are two processes that are used. The first is to spread the wet granulation onto trays, known as tray drying, and dry it in a carefully controlled oven. A concern with tray drying is that it does not always assure uniform drying throughout the batch.

The second is to “fluidize” or suspend the wet granulation in air. The fluid bed dryer system is usually more effective in generating a uniform granulate of spherical particles.

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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
- QA Laboratory
- Production
- Facility and Equipment
- Material Handling
- 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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Association of official Analytical Chemists, should be used; however specifications should be tighter where supported by historical data.

Solid Dosage forms

Sampling should be performed at the blending of the granulation stage. The granulation should be sampled and tested for uniformity, potency, and physical characteristics. Samples should be taken from specific areas of the blender, which have the greatest potential to be non-uniform. If the process calls for large or tumbler type blenders, granulations or blends can be sampled at the time of transferring product or directly from drums the product is transferred into. When sampling from drums, samples from the top, middle and bottom of each drum should be collected.

The physical characteristics that blends should be tested for are particle size and loss-on-drying if the wet granulation process is used. Particle size profiles are used to demonstrate equivalence between batches (comparability). A major physical parameter used to demonstrate equivalence between batches (comparability) is the particle size profile. Particle size profiles are particularly important for tablets made by wet granulation. The size and even the type of granule can affect the pore size in a tablet and have an effect on dissolution. Another test, typically performed on the granulation (particularly when the wet granulation process is used), is loss-on-drying (LOD) and/or moisture content.

Oral solution/suspension dosage form

Liquid products in which the product is suspended present manufacturing and control challenges. Sampling plans should include considerations to assure that separation has not occurred and sample integrity is maintained. Samples should be taken from the beginning, middle and end and should not be composited.

Facilities and equipment

Facilities and equipment should be arranged to provide protection from external influences. This includes the segregation from general traffic patterns for security and product integrity reasons (personnel, material and process flow patterns within the facility).

In-line equipment should be qualified before use according to the firm's policies and procedures. This includes permanent and/or moveable types of equipment such as air fed suites, metal detectors, monitoring devices. Actions should be defined such as precautionary measures when moving equipment from one location to another, as well as the specifications for cleaning, set-up and use.

Precautions must be taken during manufacturing to control the environment surrounding the manufacturing process in order to protect both the product and personnel. Tablets and capsules are susceptible to airborne contamination because of the manipulation of large quantities of dry ingredients. To prevent cross-contamination, the weighing, mixing, granulation, drying and/or tableting (compression) operations should be segregated and conducted in a closed environment. Air pressure differentials between processing areas should be established to assure containment of materials and to eliminate cross-contamination issues. Temperature, humidity, and dust collection control must be in place and monitored frequently to prevent cross-contamination and possible product quality impact (degradation).

Parts of the production equipment, which contact the product, should not react with, add to, or absorb the drug product. Production equipment should be checked and calibrated at scheduled intervals. All out-of-tolerance results discovered during calibration of critical

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use in the finished product

Line Clearance

Line clearance procedures to avoid product, component, labeling materials, and equipment mix-up are expected to be in place. The intended purpose being to confirm the previous batch materials have been removed, appropriate cleaning has been performed and, with the onset of the next operation, the respective processing area(s) is/are devoid of extraneous materials. It is suggested, that a checklist approach be utilized to document and verify that all mechanical and printing equipment has been broken-down, cleaned, inspected and all previous materials removed. Execution of the checklist should be by an independent person not involved with the cleaning activities. The checklist must be reviewed and inspected by another individual and final approval granted by Quality Assurance/Control prior to set-up. Quality Assurance/Control is responsible for oversight of line clearance activities.

Process Inspection Controls

Appropriate procedures are to be in place to identify and evaluate in-process materials for defects. Defects should be defined and categorized. Defects and specific acceptance criteria should be defined and utilized based on process validation data. Information obtained from data collection should be tracked and trended.

It is common industry practice to utilize in-line metal detectors to inspect tablets following compression. As part of the initial machine qualification and the resulting specifications that are defined for sensitivity settings, processing settings should be established and challenged during routine production.

Only under controlled conditions should rework/reworking be permissible. The circumstances must be defined, monitored and may require approval for each event. Each event should be clearly documented and undergo the same review processes as a routine batch. Such events should be as a result of a clearly defined and justified root cause that has had an extensive product impact assessment. It is expected that these types of events are not frequent, are trended and have corrective and preventative actions implemented.

Campaign manufacturing is a common practice. If this practice is considered acceptable controls must be apparent to ensure that if a failure does occur, all batches within the campaign are included in the investigation(s) and product assessment.

Summary

The overview of the auditor's job during an oral Solid/Solutions Area for each step of the manufacturing process is to verify that:

- the appropriate approved SOPs are being followed
- the facility is able to prevent cross contamination through personnel controls, design of the facility and equipment including the air handling system.
- the process is validated and meets acceptance criteria for critical process parameters.
- the data trail is intact with no gaps. This allows authorized individuals to make responsible decisions for release of the product.
- appropriate sampling is conducted at the correct stages of production.
- all GMP controls are in place and functioning.
- all operating personnel understand and are trained in the GMP requirements that pertain to them and perform their job functions accordingly.

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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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- Review validation documentation, process documentation, and SOPs.
 - Determine if the following topics are included in approved SOPs:
 - receipt, testing and storage of raw materials
 - detailed methods for manufacturing including equipment to be used, identified critical process parameters, acceptance criteria and specifications.
 - maintenance schedule and cleaning of both electronic (computer) and process equipment, including detailed methods of cleaning and testing, cleaning schedule for non-dedicated equipment, cleaning schedule for equipment used in campaigns, post cleaning testing for equipment release.
 - a detailed method for performing and documenting investigations of manufacturing excursions
 - a documented method for making changes in either manufacturing equipment or manufacturing processes (i.e. an approved change control procedure).
 - sampling of in-process material including the method, frequency and quantity of samples.
 - record retention policy for manufacturing and testing records.
 - Compare the approved, validated process record to the Master Formula Record and to the current Batch Record to identify any discrepancies
 - Determine if the facility is following their SOPs.
 - Using the development report for the specific product you are following, review the key decisions and rationale behind the determination of physical/chemical specifications for raw materials, selection of manufacturing equipment, choice of manufacturing process, in-process controls, and finished product specifications.
 - Review equipment cleaning validation and cleaning methods performance documentation.
 - Review personnel training records for GMP training and job skills training.
 - Use of IPC charts and personnel's authority levels to change settings on equipment if needed to bring the process back in line.
 - Mix-up prevention SOPs