

Auditing Packaging Material Vendors

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Audit Training Manual: 018

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Explanation of Topic

Packaging components

Package components are defined as Packing components critical (PCC) or Package component – Non-critical (PCNC).

In principle, there are differences between the way ‘Non-Critical’ and ‘Critical’ package component suppliers are handled from an auditing view. The differences are that suppliers of critical package components must have an on site supplier audit, where non-critical package component suppliers may only require a Supplier Quality Review (postal review).

This training module will explain some manufacturing methods for package components and key GMP principles that should be considered and reviewed during the audit.

Packaging component manufacturing

For suppliers of either printed package components or product contact components it is imperative that processes are in place to ensure the components are meeting a well defined acceptable standard.

Product contact package components can be utilized to protect and keep the medicine from deterioration. Examples include blister strips for solid dosage forms or sealed glass vials for freeze dried powders. In addition, certain components control the delivery of the drug such as metered dose aerosols.

Printed package components such as cartons, labels and leaflets, are designed to ensure the healthcare provider and patient are given the appropriate information for safe and correct use of the medicine.

Component supplier operations must be performed in a manner to minimize the risk of cross-contamination and mix-ups. Approved written procedures must be detailed and in place. They should include information for receiving, identifying, storing, handling, sampling, examining, and/or testing of materials. These procedures must be followed.

Key GMP principles to consider during the audit are:-

- Specification
- Identification and traceability
- On-line and segregation controls
- Change control
- Line clearance
- Contamination control
- Validation, Qualification or capability documentation
- Sampling
- Documentation
- Print security
- Special considerations

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Line clearance

Line clearance is an essential element in product mix up prevention and needs to focus on:

- Input materials on the line from the previous batch
- Samples and waste from the previous batch
- Documents on the line from the previous batch
- Verification that any electronic data is wiped from consoles etc.
- Clearance after maintenance activity or major interruptions as appropriate.

Line clearance activities need to be documented and cover all areas, not just the machine or line:

- The whole machine, including hoppers, conveyers, reject stations, etc
- The floor around the line
- Benches, cupboards, shelves around the line
- Pallets.

The line clearance should be documented, signed and an independent check completed and signed before the area is released for use.

Contamination control

The facilities should be designed and laid out to appropriately reduce the risk of contamination from the environment and permit effective cleaning. Personnel gowning and hygiene practices are part of contamination control efforts that may be applicable.

The supplier should define the appropriate environmental conditions for handling and storage of the component(s) being manufactured. Guidance for minimum conditions can be found in PS 9000 Pharmaceutical Packaging Materials, as well as programs such as ISO 9001:2000 and ISO 9004:2000 for pharmaceutical packaging materials.

Validation and Qualification

Ensure the processes are adequately validated, qualified and/or demonstrated according to the quality critical parameters of the component being manufactured. This may be demonstrated in the form of capability studies.

Sampling

There should be an SOP that defines package component sampling. The components sampled should be representative of the batch and sampling should be conducted to prevent contamination from the sampling method.

Any packaging materials that meet appropriate written specifications should be formally approved and released for use. Any components that fail to meet such specifications must be rejected to prevent distribution.

Samples taken away from the line should not be returned to the line. They should be reconciled and placed in dedicated containers for destruction.

Documentation

The appropriate SOPs and batch records must be followed when documenting any information or data associated with a component manufacture. Other pertinent types of

documentation include:

- Records of how and who set up a particular machine

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Printing plates should be uniquely identified and access controlled. Verification of the print impression should be completed against a controlled master version as part of the make-ready and approval to run the job.

If reference standards, such as color matching books are used, they should be appropriately controlled.

Gang printing is not a preferred practice due to the potential risk of mix-up. However, if performed stringent controls should be in place.

To reduce the risk of unprinted material in the finished component, processes should be employed in the printing process. The processes include double sheet detectors for sheet fed printing machines and sensors that alarm or highlight depression of printing plates from the print medium.

In addition, systems should be evident to ensure material that is out side of print registration or images with ink starvation are securely flagged for segregation and removed.

For manufacturer/suppliers who supply labels on reels, in the case of missing labels these should not be replaced and the number of splices allowed per a reel should be defined.

Where digital printing is utilized, processes should be controlled to ensure the correct electronic artwork files for the job are in the digital printing press and there are security measures for printed products.

Special considerations

Braille

Where Braille has been incorporated into a printed package component there shall be a system for ensuring symbols meet appropriate regulatory and market requirements and comply to specifications for size and embossed height.

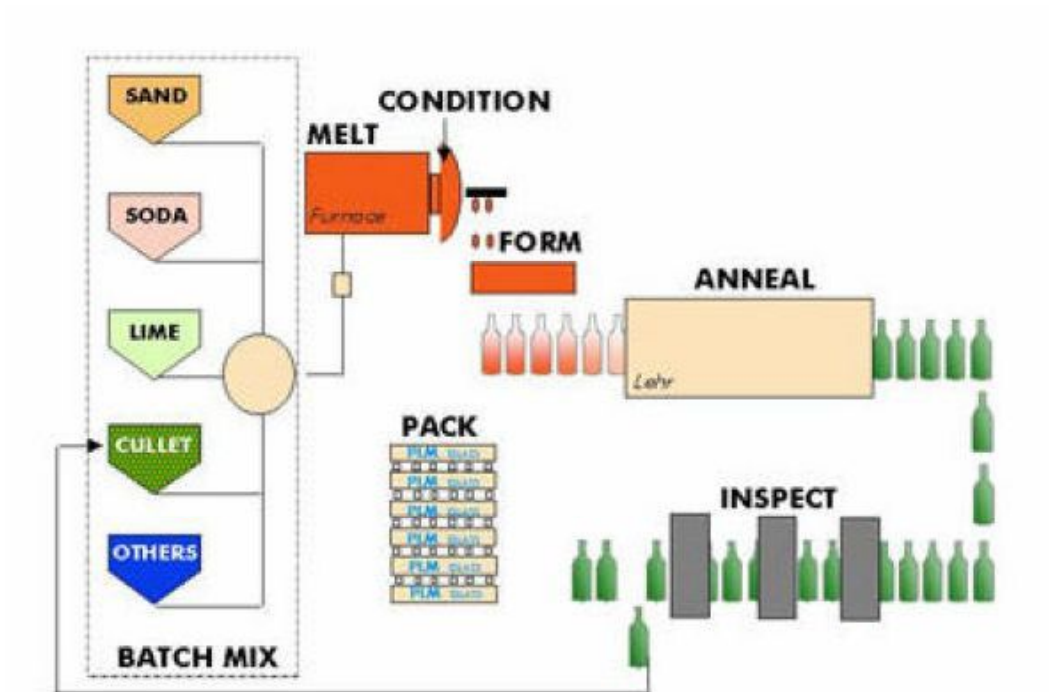
Counterfeit

It is important that basic security at the suppliers is followed to ensure that all print media including waste is stored securely and render unusable prior to secure disposal. The preferred mode for controlled destruction of materials with proprietary information is supervised incineration. This control helps in the fight against counterfeit material. In some markets a variety of anti-counterfeiting measures have been put into place e.g. the use of holograms.

Intellectual Property

Intellectual property is the intangible property that is the result of creativity (such as patents or trademarks or copyrights). It is important that components are reviewed in relation to the registration of trademarks, copyrights or patents as this could have impact on potential future changes to specification and registration details. In the case of rubber stoppers the exact details of formulation may not be disclosed by the supplier (if intellectual property) and minor changes in formulation may have a direct impact on final pharmaceutical product stability. Expectations for notification/approval authority of changes by the site should be spelled out in Business and/or Quality Agreements, respectively.

Glass manufacturing



The glass production process can be said to consist of four steps:

1. The glass melt in the furnace,
2. The formation of the bottle
3. Annealing process
4. Inspection

There are in general four types of glass:

Type i. Neutral glass Borosilicates glass – The borosilicate glass is any silicate glass having at least 5% of boric acid in its composition. Due to its properties, this is the glass commonly used for ampoules and vials in the pharmaceutical industry.

Type ii. Soda lime Silica glass Aqueous parental use where pH is lower than 7. Surface treated (e.g. sulphated)

Type iii. Soda Lime Silica - only moderate hydrolytic resistance. Non-aqueous parental use. Aqueous oral products.

Type iv. Soda Lime Silica – Low hydrolytic resistance. Non-aqueous solids for oral use. Applications such as for oral liquids.

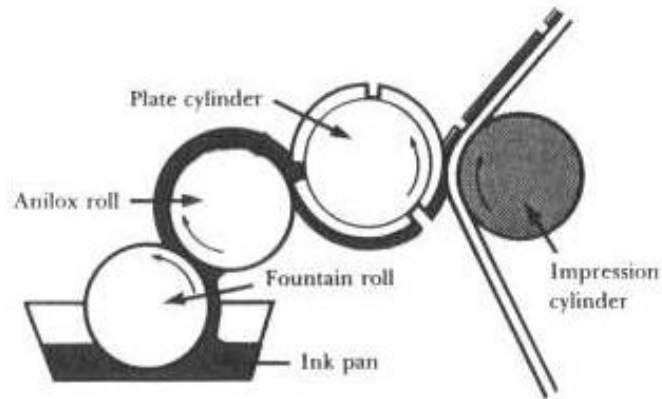
Some quality aspects to consider during the audit are:

- Glass formation and ratio of raw materials in the furnace. For example, the level and quality of cullet.

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is pulled through a series of stations, or print units, each with a single color. The various colors normally Cyan, Yellow, Magenta and Black build up the various tones by overlaying of these basic colors. The plates are flexible and are positioned around a plate cylinder.

If a step and repeat process is employed to replicate images of artwork across a plate to cover the web of print media, there should be appropriate steps in place to ensure that all such images are an exact copy of the approved artwork and no adulteration of the artwork happens during the step and repeat process.



After printing the printed sheets or reels are normally guillotined or die cut to provide the product of the appropriate size. See print security section above for quality aspects to consider during the audit.

Syringe Manufacture

Diagram of a hypothermic syringe, retraction of the plunger creates the vacuum to draw up materials, which can then be discharged by pushing on the plunger. Its rubber head makes an airtight seal against the walls of the barrel.

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- Verify each line is physically separated or segregated from each other.
- Verify the manufacturing process and dress discipline is suitable for prevention of contamination.
- Verify containers used for filling are clean before use.
- Verify line clearance procedures have been thoroughly followed before a new order/batch is introduced.
- Verify non-conforming raw materials, not suitable for use, have been identified and removed from the area and is secure.
- Verify samples are not returned to the line.
- Verify the correct order is on the line, and if approved changes have been made, they are clearly indicated.
- Verify all in-line controls are being conducted.
- Verify unprinted material, defect material and material not meeting the specification is securely segregated throughout the process to avoid mix-ups.
- Verify product, waiting to be packed, is clearly marked and segregated from the product that is being packaged. For example, printed and non-printed material labels.
- Verify that before raw materials are delivered to the line, they have been identified and released to the approved specification.
- Verify the materials and personnel flow is adequate to prevent a mix-up.
- Inspect cleared packaging component areas and verify that all materials have been removed from the area, including refuse.

- Perform a walk through of the area where raw materials are received, issued and stored.
 - Ensure current specifications are accessible, agreed, approved and utilized.
 - Ensure environmental controls are in place to maintain temperature and relative humidity at acceptable levels where temp/RH sensitive materials are stored.
 - Ensure the area is appropriately secure and materials are stored in segregated containers or locations.
 - Verify that access to the storage area is limited to authorized personnel.
 - Ensure sufficient secure control of material of non-conforming product.
 - Ensure all raw material is adequately labeled as to their identity and there is an unambiguous system for material status.
 - Ensure that there is a system so materials are not used outside the recommended shelf life.

- Ensure that there is an approved acceptance procedure for all raw materials.
 - Verify written approved procedures exist and are current.
 - Verify incoming materials have a unique reference number for identification.
 - Verify incoming materials are tested/inspected and undergo an approval process.
 - Verify materials that fail to meet acceptance specifications are rejected and quarantined.
 - Ensure documentation exists for the receipt of each shipment of materials which includes:
 - Receipt
 - Examination or testing status (either acceptable or rejected).

- Ensure that all personnel are trained and qualified to perform their function.
 - Review training records for selected individuals to ensure that they have received adequate GMP training and job skills training.
 - Ensure that there is a written procedure describing the training program and the steps needed to qualify for the job.