

# Auditing a Packaging and Labeling Operation

<b>Title: Auditing a Packaging and Labeling Operation</b>					
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## Audit Training Manual: 19

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**Primary packaging material:** The packaging, which is in direct contact with the Formulated Product, Intermediates, Excipients and APIs (including devices for delivering dosages).

**Printed packaging materials:** packaging materials that are printed and/or otherwise decorated.

**Reconciliation:** the act of ensuring that the quantity of issued labels equal the quantity used plus the returned labels and scrapped labels, within narrow preset limits.

**Secondary packaging material:** The packaging, which is not in direct contact with the Formulated Product, Intermediates, Excipients & APIs - usually contains the Primary Pack.

## Explanation of Topic

### **What are packaging and labeling operations?**

Packaging and labeling operations are designed to ensure that the finished drug product is free from damage, accurately labeled, and contains what is indicated on the package. The main purpose of labeling is to communicate essential information about medical products to health care providers and patients. Packaging and labeling operations must be performed in a manner to minimize the risk of cross-contamination and mix-ups. It is a fact that a large percentage of all product recalls are caused by errors of packaging or labeling.

Labeling and packaging materials should be representatively sampled, and examined or tested upon receipt and before use in packaging or labeling of a drug product. Any labeling or packaging materials that meet appropriate written procedures may be approved and released for use. Any labeling or packaging materials that fail to meet such specifications must be rejected to prevent their use in operations.

Approved written procedures must be detailed and followed. They should include information for receiving, identifying, storing, handling, sampling, examining, and/or testing of labeling and packaging materials.

Appropriate procedures and systems must exist which guarantee that all labeling conforms with marketing, regulatory, legal, research, technical and quality requirements. The patient is depending on the product that they receive to be the correct strength, the correct product, and free from contamination. If the package has been misbranded, or mislabeled, it may cause the patient harm. That is why it is important that drug products have been strictly controlled during packaging and labeling operations.

When performing a Quality Assurance audit, the GMP Systems approach should be used. The following systems, at a minimum, should be reviewed:

- Packaging and Labeling
- Quality System
- Material System

The following parts of a packaging and labeling operation will be further explained in this section.

- Essential packaging and labeling information

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the storage area.

- Bulk tablets should be clearly labeled and transported and stored with tamper evident seals and identity ensured before packaging
- Line clearance procedures should be thorough and performed according to a detailed checklist with two persons involved
- Packaging lines should be equipped with code readers. Codes should be entered via a master. Doing it from a label, carton or leaflet could result in a 100% of the printed component being wrong. During packaging code readers should be checked regularly.
- During packaging, checks should also be made to ensure criteria for rejection are met. Samples and rejects should never be returned to the packaging line.
- Limits for yield should be in place and justified.

### **Cross contamination**

The risk with regards to containment and prevention of cross contamination during packing operations should be assessed.

Special considerations and any regulatory requirements need to be followed when packing products such as Beta-Lactams, hormones and cytotoxics.

The risk approach normally includes:

- Consideration of other products being packed in the facility or at the site.
- Dedicated facility/packing line where appropriate.
- Design decision of packing line to prevent cross contamination.
- Design of utilities including HVAC.
- Movement and flow of people and products.
- Equipment selection and use.
- Cleaning validation and methods employed.

### **Packaging Order**

Before packaging can take place, an approved Packaging Order must be generated. The Packaging Order consists of specific instructions pertaining to the packaging and control of a finished drug product. The Packaging Order is the equivalent of a batch sheet that details the activities that must be performed both in packaging and labeling, the materials/components that must be used, and the storage conditions and special requirements for the product. The Packaging Order must contain the following:

- Product name, product-size-finish number, product strength, product form (i.e. tablets, suspension, etc), Code Number, Package Size (Quantity, weight, or volume of product in final container), Expiration Date.
- Finished lot bulk number
- Theoretical Yield
- A list of all packaging supplies and labeling used in the processing of the lot, including:
  - The name and component number and lot number (if applicable) of each packaging and labeling component
  - The quantity required
  - Special handling and usage notes
- Detailed packaging instructions
  - Line clearance checks
  - Directions for receipt and identity check of materials
  - Directions for filling and packaging operations
  - Directions for labeling
  - Process control instructions and acceptance limits

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examination must be performed by one person and independently verified by a second person.

- Monitoring of printing devices on, or associated with, manufacturing lines used to imprint labeling upon the drug product unit label or case to assure that all imprinting conforms to the print specified in the batch production record.

### **Documentation**

The appropriate SOPs and packaging batch records must be followed when documenting any other information associated with packaging or labeling. Other pertinent types of documentation include records of:

- who has set up a particular machine
- how they have done it
- adjustments or repairs
- second checks

Batch and/or packaging documentation must include:

- Exactly what has been done
- What has been used
- When the operation was performed
- Who performed the operation

### **Reconciliation**

Reconciliation limits must be established based on process history and supplier capability. When reconciliation limits are exceeded, a formal investigation must be initiated. The reconciliation must consist of a comparison between the theoretical usage (based upon output) and actual usage (based upon actual counts, where possible). Validated electronic counting equipment data may be used to determine usage. Any discrepancies that are outside the acceptable limits must be investigated and satisfactorily accounted for prior to Quality Assurance release.

Once the production order has been finished, it should be held in a hold status/unreleased status until approved by the QA/QC department and final release conditions have been satisfied.

### **Rework**

Appropriate SOP's should be in place describing how the supplier handles rework activities. Product for rework should be clearly marked and stored in a safe and secure manner until used. The rework activity should be clearly defined in an approved protocol or batch sheets. The rework documentation could include but not is not exclusive to:- Packing order details, details of rework activity, details of any inspections, acceptance criteria, line clearance, reconciliation.

### **Cleaning and Line Clearance**

Cleaning and Line clearance are essential element in product mix up prevention. A packaging and labeling process will start with line clearance and terminate with cleaning. Cleaning and line clearance need 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
- Clearance after maintenance activity or major interruptions as appropriate.

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- Verify that packaging and labeling materials not suitable for use have been removed from the area.
  - Verify that samples are not returned to the line.
  - Verify that the correct Packaging Order is on the line, and if approved changes have been made, they are clearly indicated.
  - Verify that all finished labeled product is inspected.
  - Verify that all in-line controls are being conducted.
  - Verify that product waiting to be packed is clearly marked and segregated from the product that is being packaged.
  - Verify that labels are transported in a container that segregates different types of labels.
  - Verify that the material and personnel flow is adequate to prevent a mix-up.
  - Inspect cleared packaging and labeling areas and verify that all product, labels, and packaging materials have been removed from the area, equipment and trash.
- Perform a walk through of the area where labels are issued and stored.
    - Ensure that the labeling area is appropriately secure and the labels stored in segregated containers or locations.
    - Ensure that there is adequate storage for labels and labeling, both approved and returned labels after issuing.
    - Verify that labels and other labeling materials for each different drug product, strength, dosage form, or quantity of contents are stored separately with suitable identification.
    - Verify that access to the storage area is limited to authorized personnel.
    - Ensure that there is sufficient control of labels which are similar in shape, size, and color for different products.
  - Ensure that there is a system in place to control the issuing of printed components, including the examination of issued labels and that a reconciliation process for used labels is in place.
    - Verify that there is a written and approved procedure.
    - Verify that only authorized personnel issue labels.
    - Verify that all printed materials have been examined for identity and conformity to the labeling and packaging requirements as specified in the master or product records.
    - Verify that there is a record of this examination.
    - Ensure that there is a written and approved procedure for reconciliation. This procedure should include:
      - a method for reconciling the quantity of issued, used and returned.
      - a pre-set limit for discrepancies or means to determine the limit.
    - Verify that a documented procedure is in place that allows uncoded materials to be returned to stock.
    - Review label/labeling procedures and records.
  - 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 an operator.
  - Ensure that there is an approved acceptance procedure for all packaging and labeling materials.

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- conformance to packaging specifications.
- Ensure that filled, unlabelled containers are controlled.
  - Verify that approved procedures and controls are in place to identify unlabeled filled containers or packages.
  - Verify that unlabeled filled and sealed packs are labeled as soon as possible after filling.
  - Verify that approved procedures are in place to prevent any mix-ups or mislabeling from occurring.
- Ensure that there are adequate packaging records including specimens of all labels used.
  - Verify that packaging records contain the following:
    - Listing of equipment used in packaging operations.
    - Evidence of line clearance.
    - The dates and times of packaging operations.
    - The signature of persons responsible for the packaging operations,
    - Inspection of the packaging areas and equipment for suitability and cleanliness.
    - The initials of operators involved in packaging operations.
    - The name, item code, quantity required, and samples of packaging supplies and labeling with lot number and expiration date affixed.
    - Records of checks for identity of bulk drug products, packaging supplies, and labeling.
    - Signature of qualified and trained staff members performing inspection of packaging lines.
    - A record of market package samples taken.
    - Accountabilities for bulk drug product, packaging supplies, and labeling, including amounts used, destroyed, or returned to stock.
    - Detailed information about deviations from normal packaging steps, unusual situations, and problems. These situations may require a complete investigation, and where possible, assignment of cause, and corrective actions.
  - Ensure that there are established accountability limits.
    - If accountability limits are exceeded, ensure that an investigation is initiated.
- Ensure that there is a system for destruction of labels and packaging materials.
  - Verify that the firm has an approved procedure for destruction of labels which includes:
    - Method of destruction
    - Documentation for the destruction
  - Verify that obsolete and outdated label, labeling, and other packaging materials are destroyed with accompanying proper documentation.
  - Verify any unused batch-coded packaging materials are accounted for, destroyed, and quantity and destruction documented.
- Ensure that complete investigations are performed and documented for any unexpected discrepancy.

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is to run to ensure that:

- All materials and components from the previous job have been removed
  - All line and area cleaning has been completed and checked
  - All clearances have been approved and authorized
  - All necessary paperwork has been issued for the next job
  - The details of the new job are correct
  - The line has been set up correctly
  - All machine settings and counts are as specified on the packing record
  - All containers are intact, undamaged, clean and free from any extraneous contamination, kept covered until such time as they need to be loaded onto the machine
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- Ensure that product sampling frequency is established, justified, and includes documented checks of:
    - Torque
    - Induction or heat seal
    - Weight
    - Packaging
    - Printing
  
  - Ensure that there are systems in place to control areas with product exposure to the environment and prevent cross contamination such as:
    - Appropriate HVAC system
    - Independent air handling units
    - Appropriate personnel controls
    - Cleaning regime