Packaging Control

- GMP
- FDA
- Quality
- Traceability
- Safety
- Effective
- Purity
- Compliance
- Regulations
- Guidelines
**Training Outcome of the Module:**

Customers of pharmaceutical products expect products that are safe and effective. One of the ways to ensure that products are safe and effective is by producing finished products that are correctly identified. Product and labeling mix-ups can result in potentially serious consequences.

As such, GMP rules require that products rules be correctly identified with the correct name, ingredients, strength, and batch information. There must be no unspecified components present.

On completion of this module, you will be able to:

- Define what is meant by mislabelling
- State the critical GMP requirements for packaging controls
- Describe the GMP controls for pre-printed matter
- Identify the GMP requirements of selling up a packaging line
- State the importance of online controls
- Perform basic reconciliation calculations

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**INTERNATIONAL GMP**

Outside the US, almost all regulatory agencies have standardized and harmonized to the EUGMP rules and guidance for medicinal products. Some countries, such as Canada, still maintain a country-specific code of GMP, which is very similar to the EU GMP rules.

In this training program, we use the term 'International GMP rules" to refer to the group of rules, guidance, and codes that are based on the EU GMPs. If there are specific differences that are relevant to the module, it will be indicated as such.
Introduction:

Double the dose does not mean twice as effective, because different drugs have different side effects at different strengths. Mislabeling, or mixups, of medicines has historically accounted for about 253 of all drug recalls.

Accurate labeling of medicines is critical to patient health. Therefore, manufacturers pay particular attention to get the right medication and strength into the right container with the correct labels and instructions for use. Any error here could cost lives, and will certainly result in recall.

What do the GMP rules say?

US FDA CFR 211

Sec. 211.130 Packaging and labeling operations (extract)

There shall be written procedures designed to assure that correct labels, labeling, and packaging materials are used for drug products; such written procedures shall be followed. These procedures shall incorporate the following features:

(a) Prevention of mixups and cross-contamination by physical or spatial separation from operations on other drug products.

(d) Examination of packaging and labeling materials for suitability and correctness before packaging operations, and documentation of such examination in the batch production record.

(e) Inspection of the packaging and labeling facilities immediately before use to assure that all drug products have been removed from previous operations. Inspection shall also be made to assure that packaging and labeling materials not suitable for subsequent operations have been removed. Results of inspection shall be documented in the batch production records.
International GMPs

Chapter 5 Production
Packaging materials (extract)

5.44 When setting up a program for the packaging operations, particular attention should be given to minimizing the risk of cross-contamination, mixups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation.

5.47 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the Packaging Instructions.

Top reasons for drug recalls

Product recalls can cast hundreds of thousands of dollars can damage the brand integrity of a supplier and harm the relationships between manufacturer contract packager and retailer or end consumer.

Three of the top reasons for drug recalls are labelling issues.

- Sub-potent (single-ingredient drugs)
- Impurities / degradation products
- Temperature abuse
- Lack of assurance of sterility
- Correctly labelled product in incorrect carton or package
- Failed USP dissolution test requirements
- Labelling illegible
- Label mixup
- Chemical contamination
- Microbial contamination of non-sterile products
Marketed without an approved NDA/ANDA

Stability data does not support expiration date

Part I: Potential Mislabeling

Packaging mix-ups, which are often called "mislabelling", are of the most common causes for recoil of medicines. Particular care is required in the packaging areas to ensure that batch numbers, expiry dates, correct labels, correct cartons, and correct product information leaflets are assembled with the right product every time.

When packaging rework must occur, full packaging record documentation, complete line clearance, and oil normal controls must be used.

It is also a GMP rule that products that are mislabeled should never be "over-labelled". This is because it is very easy to make an error in this rework, or it's possible that the over-label maybe dislodged later, causing the product to be mislabeled once again.

What do the GMP rules say?

US FDA CFR 211

Sec. 211.130 Packaging and labeling operations.

There shall be written procedures designed to assure that correct labels, labeling, and packaging materials are used for drug products; such written procedures shall be followed. These procedures shall incorporate the following features:

(a) Prevention of mixups and cross-contamination by physical or spatial separation from operations on other drug products.

(b) Identification and handling of filled drug product containers that are set aside and held in unlabeled condition for future labeling operations to preclude
mislabeling of individual containers, lots, or portions of lots. Identification need not be applied to each individual container but shall be sufficient to determine name, strength, quantity of contents, and lot or control number of each container.

(c) Identification of the drug product with a lot or control number that permits determination of the history of the manufacture and control of the batch.

(d) Examination of packaging and labeling materials for suitability and correctness before packaging operations, and documentation of such examination in the batch production record.

(e) Inspection of the packaging and labeling facilities immediately before use to assure that all drug products have been removed from previous operations. Inspection shall also be made to assure that packaging and labeling materials not suitable for subsequent operations have been removed. Results of inspection shall be documented in the batch production records.

International GMPs

Chapter 5 Production
Packaging materials {extract}

5.44. When setting up a program for the packaging operations, particular attention should be given to minimizing the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation.
5.55. Products which have been involved in an unusual event should only be reintroduced into the process after special inspection, investigation and approval by authorized personnel. Detailed records should be kept of this operation.

Overview

A product is "mislabeled" if the labelling and packaging information does not accurately reflect the contents of the container. For example, if a label indicates that a bottle contains 100 capsules, but the bottle only contains 99 capsules, this is classified as a case of mislabeling.
A more extreme, and potentially dangerous example, is if the product was stated as being "tamper-evident", but there is no evidence of tamper-proof seals.

It would also be mislabeled if it is not in conformance with the marketing authorization and claims. As part of product manufacture, companies must register the product’s labelling details with the regulators. If there is any deviation from these label specifications, the company is in breach of regulations.

**GOOD TO KNOW - ORIGINS OF TAMPER-EVIDENT PACKAGING**

In 1982, a deranged person in the US sabotaged Tylenol by injecting cyanide into capsules in supermarkets, which eventually killed 6 people. The FDA responded by making tamper-evident packaging a legal requirement for over-the-counter products, and the Federal Anti-Tampering Act passed in 1983 made it a crime to tamper with packaged consumer products.

**Packaging controls**

In order to prevent mix-ups in packaging, there are GMP rules in place concerning all areas of packaging materials and operations. According to PIC/S, these controls include:

- control over purchase, handling, storage, and segregation of printed packaging materials
- line clearances and identification
- packaging verification
- ensuring the containers are clean prior to filling
- labelling immediately after filling
- checking and recording of the printing operation
- on- and off-line label printing controls
- using labelling that is resistant to fading or erasing
Many mislabeling incidents commence with the wrong issue of labels or other printed matter from the store.

The GMP rules clearly state that each issue of printed matter from the store must be accompanied by requisition paperwork and that there is a cross-check that labels match the documented request before issue.

The reason for this is the issue is the first point of control. It is much better to prevent incorrect labels being issued in the first place rather than finding them (or not) later on. Mislabeling can cause incorrect consumption or patient medication, which can result in serious injury or even death of patients.

**What do the GMP rules say?**

**US FDA CFR 211**

Sec. 211.130 Packaging and labeling operations. (extract)

There shall be written procedures designed to assure that correct labels, labeling, and packaging materials are used for drug products; such written procedures shall be followed. These procedures shall incorporate the following features:

(a) Prevention of mixups and cross-contamination by physical or spatial separation from operations on other drug products.

(d) Examination of packaging and labeling materials for suitability and correctness before packaging operations, and documentation of such examination in the batch production record.
International GMPs

Chapter 5 Production
Packaging materials (extract)

5.40 The purchase, handling and control of primary and printed packaging materials shall be accorded attention similar to that given to starting materials.

5.41 Particular attention should be paid to printed materials. They should be stored in adequately secure conditions such as to exclude unauthorized access. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups.

Packaging materials should be issued for use only by authorized personnel following an approved and documented procedure.

Overview

There are GMP controls over how manufacturers handle printed material. Printed matter should be verified, kept separate, and secure at all times. This ensures that the distributed product does not result in recall or withdrawal from the marketplace. These measures help to protect patients from taking the wrong medicines.

The term “printed matter” includes:

- Labels for containers (rolls of labels and cut labels)
- Package leaflets (inserts and outserts)
- Labels for cartons or packaging
- Printed containers (e.g. lubes)
GMP controls at the printers

Pharmaceutical labelling suppliers are a major component of a successful packaging and labelling process. Their adherence to change control and GMP compliance should be as strong as for the manufacturers themselves.

Routine audits of the printed matter suppliers to GMP standards are needed. The audit should focus on the printer's line clearance practices, the printer's counting accuracy and an acceptable system for handling and disposing of waste.

Printers should follow written and GMP-approved operating procedures in order to tighten packaging and labelling control. Being able to trace materials and good record keeping are needed to help prevent mixups. Where different batches of printed material are being produced at the same time, they should be physically separated from one another to avoid mix-ups.

Other in-process controls at the printers include:

- using identification numbers that are unique to each revision
- optical bar codes for verification
- artwork control
GOOD TO KNOW – “MAKE READY”

A common occurrence in the printing industry is the use of "make ready", which refers to the first few sheets or labels to pass through a printing machine before the actual run starts.

There is a natural desire to save on maternal waste by minimizing make ready, or using it to set up other processes, but the wiser course of action is to discard it at each step in the run. The potential savings of reducing waste are awarded by the cost of an improper matching of packaging materials.

Receiving printed matter

Although seemingly removed from manufacture, the process of receiving printed matter at the inward goods bay is crucial for producing a quality product. Inward goods must ensure that the right printed matter is received, so that the correct printed matter is eventually released to the packaging area.

When the printed matter arrives from the printers, it must be given its own unique identifying number, and then placed into quarantine.

Following receipt and quarantine, printed matter is examined and verified by QC against standard specimens and specifications in order to avoid any mix-ups or errors. QC must take particular care with sampling and testing because many labels, cartons, and leaflets look alike. Packaging and labelling samples should not be returned to inventory.

Printed matter can be released for use by the Quality Department only after it has passed inspection.
## RECEIVING PRINTED MATTER

- Roll labels must be counted either on receipt or at issue.
- Supplier counts are not acceptable unless the supplier is specifically qualified and supplier certifies the exact count for each roll.
- Supplier numbering of labels is an acceptable alternative.
- Cut labels must be counted and effectively verified by the manufacturer because of the risk of mix-up.

- Printed matter must be quarantined from use until it has been thoroughly quality-controlled.
- Quarantining involves placing the received material into a locked, separated store, secure from unauthorized access.
- All personnel, when they handle printed matter, should double-check that the "Quarantine" label has been replaced by an "Approved for use" label. If it hasn’t, do not use the printed matter.

Sampling plans are used by QC in order to specify the number of samples of printed matter to be taken. There are several types of sampling plans QC use, e.g. statistical, targeted, and zero acceptance number. Although QC use all of them for printed matter in some respects, the reasons why each are chosen is beyond the scope of this module.
Suffice it to say, sampling plans for printed matter account for at least the following:

- the quantity and quality of printed matter received
- the quality of printed matter required
- the nature of the material (e.g. primary and/or printed materials)
- the production methods
- an audit of the printed matter supplier
Labels and cartons (outers) can be coded with batch numbers and expiry dates either offline or online. For offline coding, a specific packaging record is required, along with all the usual checks and clearances. Online coding is usually done at the time when the printed matter is applied to the primary packaging.

Occasionally, unused, uncoded printed matter is returned to store for later use. The return process requires specific checks of its own.

### GMP Controls Over Printed Matter Storage and Coding

| **Online Coding** | Some manufacturers elect to code the batch number and expiry dates "offline", i.e. in a separate production step, in a process called printed mailer coding. This step requires all the line clearances and double-checks that are also used on the packaging line itself. Correctly-coded printed mailer may be either returned to the printed mailer store for reissue or transferred directly to the packaging line. |
| **Line Check** | Before commencing packaging, a line clearance should be done to ensure that there is no potential for mislabeling. The line clearance involves two things:  

- complete removal of all previous product documentation and printed matter from the previous belch, followed by;  
- introduction of the new printed matter to the line with a double-check that the correct printed matter has been selected and presented to the line. This check must be recorded and authorized in the packaging record. |
During the actual packaging, many things may go wrong, therefore, frequent online checks are necessary.

- When printed matter is first presented to the line, ensure that only the correct material has been introduced.
- When additional packaging materials are bought to the line, double-check them for correctness.
- When the line stops any reason, double-check the items on startup.
- When automatic online verifiers are used, verify that they are reading correctly before use.

Some companies elect to directly print the batch number and expiry dates "online", i.e., apply the information at the same time the printed matter is assembled with the product, in order to minimize the chance of mix-ups prior to labelling. This approach requires additional controls in place.

It is important to ensure the setup for online coding is double-checked to verify that only the correct batch number and expiry date is programmed in. As the packaging run progress, it is important to also check that the inking or printing has not deteriorated, which could leave units incompletely coded or not coded at all.
| ISSUE | Printed matter is to be checked against the work order to verify:  
|       | - the assigned product and lot number  
|       | - the printed matter code and version number  
|       | - the batch number and expiry date (if printed matter is already coded) |
| RETURN CONTROL | Printed matter returned to the store should only be handled by authorized personnel. The person returning the printed matter should never directly put it back into storage.  
|       | Extreme core must be taken when returning printed matter to storage because it is well-known that mix-ups occur if returned items are placed in the wrong storage locations.  
|       | The alternative to returning unused printed matter to the store is outright destruction. If the coded printed matter isn’t used, it must be destroyed, because it cannot be subsequently used. When printed matter is destroyed, it must be done so in a secure manner, accompanied by a signed record of destruction. |
Some organizations will not return printed matter to the store, because of the potential to mix up the returned item.

It is a GMP regulation that coded printed matter is never returned to the store for reuse. The reasons for this should be apparent, as coding is always unique to a batch.

**Part III: Line Clearance & Setup**

In a busy packing hall, there are generally many products being processed at once. Unless there are specific GMP controls in place, it is inevitable that a rogue item of printed matter will eventually end up on a different product. This may not get detected later, and could injure patients and cause a recall. Proper line segregation helps to physically separate different printed matter, much of which looks similar.

A combination of physical segregation, double line checks when new printed matter arrives, and detailed line clearances are critical GMP labelling controls.

**What do the GMP rules say?**

**US FDA CFR 211**

**Sec. 211.130 Packaging and labeling operations. (extract)**

There shall be written procedures designed to assure that correct labels, labeling, and packaging materials are used for drug products; such written procedures shall be followed. These procedures shall incorporate the following features:
(a) Prevention of mixups and cross-contamination by physical or spatial separation from operations on other drug products.

**International GMPs**

**Chapter 5 Production**  
**Packaging operations (extract)**

5.44 When setting up a program for the packaging operations, particular attention should be given to minimizing the risk of cross contamination, mix-ups or substitutions.

Different products should not be packaged in close proximity unless there is physical segregation.

5.45 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents previously used; if these are not required for the current operation.

The line-clearance should be performed according to an appropriate check-list.

**Overview**

Line clearances are used in the labelling and packaging area as another control to prevent mix-up of product, the following steps must be conducted and verified prior to the start of packaging and labelling operation:

- Clean the area and machines,
- Remove all previous products from the area and machines.
- Remove all waste from the area and machines.
- Reconcile all printed material and product from the previous batch.

Once the above steps are complete, it must be documented that the area and machines are inspected and found to be clear of all previous product.
**Line clearances**

Before commencing any filling and labelling operation, the line should be thoroughly examined following a standard operating procedure to ensure that all materials, product, labels and records from previous operations have been removed, the person responsible should initial the batch record to show that this check has been carried out.

The line should be clearly labelled to show the product (and strength of product) to be packaged. Any label counters or code readers should be tested to verify that they are working correctly.

Labelling and packaging material should be carefully checked to ensure that they match the descriptions in the batch packaging records.
1. Verify that the correct reel has been introduced.
2. Monitor the label out feed to ensure that it is not jammed and no labels remain on the reel.
3. Labels can easily become jammed in star wheels. Always check around the conveyor belt and star wheels for surplus labels.
4. Check beneath the packaging machine for any printed matter that may have fallen down.
5. Set up the barcode verifier and test that it is reading correctly before commencing.
6. Check for labels that may have adhered to the belt.
7. Always check the "first off the line" to ensure that the labelling is correct.
8. Check beneath the packaging machine for any printed matter that may have fallen down.
9. Make sure that the reject box is empty.

**Performing a line setup**

Before a new packaging and labelling operation can begin, a line setup must be performed, including:

- verifying that the line has been cleared
- assembling the material needed for the new operation
- verifying that each container of bulk material is approved for use
- verifying that all printed matter conforms to the descriptions in the batch record
- labelling the line with the product name and strength

To prevent packaging mix-ups, GMP rules require that lines be physically integrated. This generally means partitioning between adjacent production lines.
Note the glass wall between the two packaging lines. This prevents materials from being inadvertently mixed up between the lines and operators from passing materials back and forth from line to line.

**GOOD TO KNOW – ISSUE WITH MULTIPLE PRODUCTION LINES**

A common occurrence is to misdirect packaging materials where there are multiple production lines in operation.

Besides the normal automated quality controls on the production equipment, misdirection of packaging materials can be minimized by assigning a color code to everything associated with particular production lines (e.g. the "blue" line, the "red" line).

The containers or totes used to issue packaging and labelling to the production line can be color-coded - and even the operator SOP manuals - and operators can be trained to notice, and react to, the presence of wrongly colored tote bins. This simple procedure provides an extra measure of quality control.
Part IV: Online Controls

On-line controls for the packaging line must be in place. Items that should be checked before, during or after operations are that:

- lines and equipment have been cleared of bulk material, labeling and packaging materials and documentation from previous operations, including any computer screens or systems holding information pertinent to the batch.
- the general appearance of finished packages is satisfactory
- the packages are complete
- the correct product and packaging materials are being used
- over-printed details are correct and clearly readable
- all line monitors, indicators, and readers are working or have worked correctly

Special attention should be paid to checking the accuracy of variable information, such as batch numbers and expiration dates to packaging components on line. Printed and embossed information on packaging materials must be clear, easy to read, and resistant to fading or erasing.

In process test equipment e.g. Leak test equipment to realize integrity of blister sealing should be on the equipment and maintenance schedule. The in process testing should be completed as appropriate to demonstrate the integrity on the blister is maintained throughout the packing order. Any failures should be documented, investigated and appropriate actions taken.

Special controls should be applied to the management of trial and experimental packing work to ensure the same level of compliance and assurance is applied for this type of work around packing, documentation and labeling compared to routine work.

What do the GMP rules say?

US FDA CFR 211
Sec. 211.130 Packaging and labeling operations. (extract)
(d) Examination of packaging and labeling materials for suitability and correctness before packaging operations, and documentation of such examination in the batch production record.

International GMPs

Chapter 5 Product
Packaging operations (extract)

5.52 Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.

Overview

During the packaging and labelling operation, GMP rules specify a certain number of necessary online (in-process) controls.

Online controls should include the following checks:

- the bulk material and printed matter
- the appearance of the product (e.g., chipped labels, particles in sterile injectable)
- the equipment used (including the label verifier)
- the count or measure of the filled container
- the label appearance and adhesion coding
- the tightness of the cap
- the seal integrity or the packs

When these checks are done by production staff, the check should be audited by the Quality Department.

Run Charts

Run charts are often used to monitor manufacturing processes. They show the:
Target Fill

- Lower specification limit (LSL)
- Upper specification limit (USL)
- Actual progressive volumes dispensed over time

For instance, 100ml bottles of a Product are being filled from a packaging line.

Following are the fill specification for the product:

- **Stated volume on bottle:** 100.0 mL
- **Target volume:** 105.0 mL
- **Lower limit (LSL):** 103.5 mL
- **Upper limit (USL):** 106.5 mL

From the Run Chart diagram below, it appears that some points are above and below the upper and lower specification limits. This would mean that the process would have to be adjusted and perhaps the batch would need to be quarantined. The run chart, though, does not provide any indication whether the process has consistent (predictable) variation, or whether it is "out of control".

![Run Chart Diagram](image-url)
Control charts

Control charts are statistical tools that are used to determine if a process is capable of performing within specification limits. Control charts also provide rules for changing or adjusting the process should it get "out of control".

A control chart is bounded by upper and lower control limits (UCL and LCL) which are calculated from the natural variation of the process. If these limits are within the specification limits, the process is termed "capable".

In this example, the control limits are wider than the specifications limits, so the process is classified as "not capable". Because the process isn't capable, action is required to bring the process back into control. If no action is taken, the process should not be used for manufacturing.

GOOD TO KNOW – CONTROL CHARTS

Packaging processes can be monitored using either run charts or control charts. A control chart is more complex to use, but provides better control over the process.

There are also specific rules about when to adjust the process and when to leave it alone. These rules are not just based on meeting packaging
specifications. Control charts are established based on statistical theory regarding process variation. If your company is using a charting approach to controlling processes, ensure that you have trained in their use and interpretation.

**Auditing a Packaging Operation controls**

During the quality assurance audit the following parts of a packaging and labeling operation must be audited.

- Essential packaging and labeling information
- Mix up risks and prevention
- Cross contamination
- Packaging Order
- On-line controls
- Sampling
- Labeling
- Documentation
- Reconciliation
- Rework
- Line Clearance

**AUDITING A PACKAGING OPERATION**

**Essential packaging and labeling information:**
The packaging and labeling must include:

- Identification of the product
- Final finished dose form (tablets, capsules, injection)
- Strength of each individual unit
| **The manufacturer, packager, or distributor** |
| **The manufacturing batch number** |
| **The expiration date** |
| **Standard dosage requirements** |
| **Frequency of dose** |
| **National Drug Code (product distributed in the US market)** |
| **Additional national requirements, if any** |
| **Storage statement** |
| **Declaration of net quantity of contents (count, weight, measure etc)** |
| **Precautions to observe if there are incompatibilities with other medical conditions or products, as well as awareness of possible side effects** |
| **Package inserts, patient information leaflets** |

**Mix up risks and prevention:**

Defects related to packaging, labels and leaflets are the most common reasons for recalls. Thus it is important to identify risks for mix-up during packaging and label operations and to ensure there are appropriate procedures in place for mix-up prevention.

Mix-ups may occur if personnel are not aware of the risk, if layout of premises or procedures are not adequate. The following should be reviewed and or considered:
Personnel should be trained in mix-up prevention.

Packaging lines should be physically separated and clearly marked with ongoing activities.

Material for packaging and labeling should be stored in a secure way preventing mix-up. Particular attention should be paid to printed primary packaging material and labels. Review how printed packaging material is controlled, received, approved, stored, dispatched, transported, used and returned. They should preferably be coded and code read in-line to check the identity. Material with additional printing – batch number and expiry date – should never be returned to 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
  - Directions for sampling
  - Handling and storage requirements
  - Special handling requirements
  - Where appropriate, an example of the relevant packaging supplies and labeling with the lot number and expiration date affixed.

**Sampling & Labelling**

Samples taken away from the line should never be returned to the line. They should be placed in dedicated containers, clearly marked. The use of cut labels should be discouraged or minimized. If cut labeling (and other loose packaging components with a pre-printed Lot Number and Expiration Date) is used, packaging and labeling operations must be following special control
All cut labels must be stored and transported in a secured container.

Controls used for routine labeling activities include:

- Use of appropriate electronic or electromechanical equipment to conduct a 100% examination for correct labeling during or after completion of finishing operations.

- Use of a visual inspection to conduct a 100% examination for correct labeling during or after completion of finishing operations or hand-applied labeling. Such 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:
Part V: Reconciliation

Reconciliation of printed matter is one of the key GMP packaging controls. The reconciliations indicate how many printed matter items are not accounted for.

It is well-known that incorrect calculations are common mistakes in this area, for example, assuming that any unaccounted for numbers must be rejects. While reconciliation limits should be tight around 100%, it isn't expected that every result is exactly that number.

What do the GMP rules say?

US FDA CFR 211

Sec. 211.125 Labeling issuance. (extract)

(a) Strict control shall be exercised over labeling issued for use in drug product labeling operations.
(b) Labeling materials issued for a batch shall be carefully examined for identity and conformity to the labeling specified in the master or batch production records.
(c) Procedures shall be used to reconcile the quantities of labeling Issued, used, and returned, and shall require evaluation of discrepancies found between the quantity of drug product finished and the quantity of labeling Issued when such discrepancies are outside narrow preset limits based on historical operating
data. Such discrepancies shall be investigated in accordance with 211.192. Labeling reconciliation is waived for cut or roll labeling if a 100-percent examination for correct labeling is performed in accordance with 211.122(g)(2).

**International GMPs**

**Chapter 5 Production**

**Packaging operations (extract)**

5.56 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.

5.57 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure should be followed if uncoded printed materials are returned to stock.

**Overview**

In a reconciliation, the quantify issued to (a known or verified count) should be compared with the sum of:

- the quantity used for good product
- the quantity used for rejected product
- the quantity used for samples
- the quantity used on documentation
- the quantity damaged
- the quantity returned

Every single measure is a count, not a calculation.

An unsatisfactory reconciliation can indicate loss of material, a gain of foreign material, a miscounting, or bad arithmetic.
GOOD TO KNOW - YIELD AND RECONCILIATION

Yield and reconciliation are two ways of looking at material balance. Yield focuses on acceptable product outputs and is usually used for production processes. Reconciliation focuses on losses or apparent gains of materials, and is usually used for labelling and packaging operations. Reconciliation compares the amount of material going into a process with the amount coming out of the process.

Calculating reconciliation

Reconciliation calculations must appear on batch records for each batch processed, and they should be calculated carefully and accurately. Estimating or fabricating figures for waste or losses in order to achieve a 100% result may result in a product recall. or worse still, injury to a customer.

Companies should try to use simple formulae and calculation steps to facilitate reconciliation.

Reconciliation results, however, are only meaningful if they can be compared to acceptable limits or tolerances. The limits should be established from a critical review of actual batch records that reflect good practices. The limits may be expressed as either the number unaccounted for or as a percentage.

Note: Weighing printed matter is not an alternative to counting. Due to the variability in paper weight, weighing the printed matter is far too inaccurate to be credible.

GOOD TO KNOW – AUTOMATED RECONCILIATION

Some companies use barcode readers and optical verification systems to minimize the reliance upon reconciliation.

However, the accuracy and reliability of these devices will need to be defended through validation and regular performance checking.
GOOD TO KNOW – RECONCILIATION USING NUMBERS

An alternative to using a reconciliation as a percentage is using an actual number of units unaccounted for. For example:

- 0 in < 5000 units
- 1 in 5,000-7,500 units
- 2 in 7,500-10,000 units
- 3 in > 10,000 units

This is a "tighter" specification, because when batches are larger, the percentage method allows for increasing numbers of unaccounted for items.
Summary

This module highlighted the importance for instituting packaging and labelling controls at a pharmaceutical manufacturer. GMP rules dictate that these controls are in place in order to ultimately protect the customer from mislabeling errors. Specific packaging and labelling controls govern:

- Printed matter (e.g., control, over artwork and printers, limited access to the label store, disposal of obsolete and rejected printed mailer)
- Validation of counting equipment
- QC sampling
- Line clearances
- Continuous monitoring of critical process parameters
- Online controls, such as:
  - Material and label identification
  - Count (or measure) of the filled container
  - Seal integrity
  - Label verifier function
  - Coding
  - Pack appearance
- Reconciliation
**TAKE THE TEST NOW**

- Number of questions: 10
- No time limit
- Allow you save and finish at a later date
- Allow you to go back and change your answer
- Attempting each question is mandatory
- Pass mark at and above 70%
- Print results and certificates