

8. Filling, packaging, and labeling

The finished product, the dosage form, must be placed in some kind of container and labeled accordingly. The container must be of a kind that does not have a negative influence on the product and must follow the relevant specifications.

Some types of containers, for example glass bottles, must be washed, possibly sterilized, and prepared as a part of the manufacturing process. In these cases there are procedures to follow and we record this in the batch record, just like all other steps of the production.

Examples of common dosage forms:



Nose spray



Eye drops



Infusion solutions



Inhalation products



Capsules



Liquid (oral)



Tablets



Effervescent tablets



Injections



Creams /Ointments



Instruction for filling
and packaging

Usage of correct
packaging and labeling
materials

Issuance of labels

Return of excess
materials

Reconciliation of labels

All containers, packaging material, and labels are treated in much the same manner as the raw materials for manufacturing. This includes supplier evaluations, receipt controls and tests, procedures for storage and handling, and traceability throughout the documentation.



Checks of labels and containers are made at the packaging. The product is also visually checked.

High requirements are applied to labels and other labeling materials since errors are common regarding these.



Batch record

Just as described for manufacturing, the filling of the dosage form in its container must be documented in a batch record. Here, we first document that the correct material is at hand and that the equipment is clean, free of residue from earlier activities, and ready for filling.

Check and tick that:

- 1 the cooling area is empty
- 2 the end of the sterile tunnel is empty
- 3 there are no bottles under the tunnel
- 4 the start of the sterile tunnel is empty
- 5 the inlet of the sterile tunnel is empty
- 6 the outlet of the sterile tunnel is empty
- 7 the dishwasher is empty
- 8 the inlet to the dishwasher is empty
- 9 it is empty on and under the tool cabinet
- 10 the working table is empty
- 11 the whole floor is empty

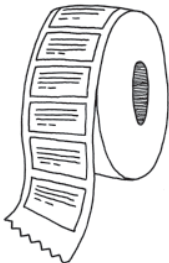
Sign that all stages have been checked

OP 1	OP 2
✓	✓
✓	✓
✓	✓
✓	✓
✓	✓
✓	✓
✓	✓
✓	✓
✓	✓
✓	✓
✓	✓
✓	✓
✓	✓
Gold	BEKO

“Line clearance” is a very important step and it includes careful checks to ensure that all materials from earlier activities are removed. It is usually carried out by one person and verified by a second person to minimize errors.

It is not unusual that filling, labeling, and packaging are done in one uninterrupted step. If delays occur between filling and labeling, there must be procedures on how the unlabeled products are to be handled and stored.

Labels and other labeling material are checked through several steps. The first check beside the controls at receipt are carried out in the storage area so that the correct amount and type are selected for the specific activity.



Labels used on pharmaceuticals for sale are checked several times on their way from receipt to a final check when ready packed



Verification of the imprint

Inspection of labeling and packaging materials


Rejected labeling and packaging material

Inspection of the line, before, during, and after manufacturing


Additional checks ensure that the correct labels and labeling material are available before the labeling begin. The unique information such as batch number and expiration date is added. This information is often called imprint and is carefully checked and documented.


During the labeling procedure additional checks such as random tests or scanning of each filled container is carried out.

Reconciliation of used material:

Released quantity	(A) <u>5000</u>
Used quantity	(B) <u>4932</u>
Rejected quantity	(C) <u>65</u>
Quantity returned	(D) <u>13</u>
Total (B + C + D)	(E) <u>5000</u> 5010 CALCULATING ERROR  2007-09-03

Contact supervisor immediately if (E) is not equal to (A)!

Calculated by:  Date: 2007-09-03

Checked by:  Date: 2007-09-03

After labeling and packaging, reconciliations are done to compare the amount of material at hand, the quantity used, and how much is left-over. If there is too much or too little material left-over additional controls are carried out since labeling material that is unaccounted for increases the risk for mix-ups

Sterile products



Requirements for the manufacture of sterile products

Some pharmaceuticals, for example intravenous drugs, must be sterile (sterility = lack of living microorganisms). For these products, sterilization is a separate step in the process usually carried out after or during filling.

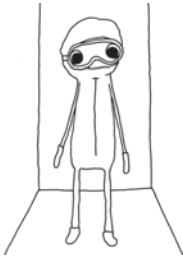
Commonly, the product is put in its container and then exposed to high pressure and heat in an autoclave (similar to a high pressure-cooker). After removing and cooling, a

label or other mark is added and the container is packed in an additional pack.

Some products are sensitive to high temperatures and cannot be autoclaved in this manner. These products are produced by an aseptic manufacturing technique. This demands very high hygiene standards, all equipment in contact with the product must be sterile, the personnel dressed in specific clean room clothing, and the facilities and ventilation must comply with high hygiene standards.

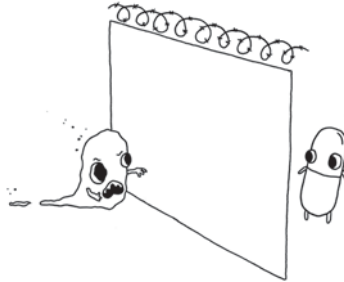


Assessment of environmental conditions



It is not just the clothing that is important but also our actions while inside the clean room, i.e. we must move slowly and carefully and avoid conversation or other activities that might generate unwanted particles

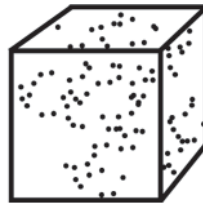
An important concept for manufacturing sterile products is to create an effective barrier between the product and everything that might threaten its sterility



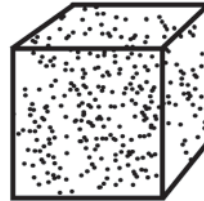
The high demands on sterile products are applicable to the entire chain of quality. The requirements for handling and storing raw materials are higher and the personnel must have special training for understanding the connection between hygiene and quality of product.

The equipment must be made of materials that can be sterilized, the facilities must be divided into areas with clothing change requirements between each one, and the environmental conditions must be measured and documented much more frequently than for non-sterile products.

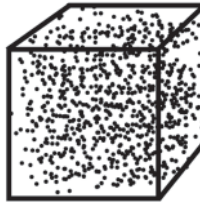
When sterile products are manufactured by aseptic technique, data from these types of surrounding circumstances is added to the evaluation made before the product is released.



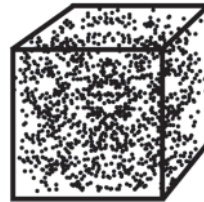
Class 100/A
ISO 5



Class 1 000
ISO 6



Class 10 000/B
ISO 7



Class 100 000/C
ISO 8

There are several classification models for different kinds of clean rooms. Depending on the type of pharmaceutical and how the product is to be used by the patient, the clean rooms follow these classifications. Each type corresponds to a certain level of cleanliness, the highest amount of particles the air may contain. ISO 14644-1 has a classification model but within the industry the A-D and 100 - 100.000 classes are also used.