Chapter 15

Inspection, Labeling, and Packaging

Objectives

The final phases of drug product manufacturing consist of a physical inspection of the primary product container and the liquid or lyophilized drug product within the container. This is followed by labeling and packaging the product for shipment. The inspection may be manual, semi-automated, or fully-automated.

What is packaging?

For parenteral drugs it consists of:

- the primary container: packaging that is in direct contact with the drug product (e.g., vial, syringe, stopper, ampoule)
- secondary packaging: packaging that is designed to protect both the product and the primary container over the life of the drug product
- labeling: this is the label applied to either the primary container, printed cartons that the primary container is placed in, or package inserts

All proposed packaging must be proven to be appropriate for its intended use. It must not only adequately protect the product but also be compatible with the product. Determining compatibility with primary packaging components is an integral part of the dosage form development process. The packaging components (glass, rubber stoppers, and various plastics) must be proven not to add or remove anything from the drug product. The specifics of product contact studies are covered in another part of this chapter.

After completing this chapter the student will be able to:

- explain the purpose of **inspection** and some related regulatory requirements.
- describe some basic **regulatory requirements and manufacturing controls related to labeling** and explain why clear, accurate, and complete labeling is important.
- identify the difference between a label used for clinical trials versus a label used for commercial production.
- identify some basic **types of packaging** used in the pharmaceutical industry.
- describe some basic **regulatory requirements related to packaging** and explain how packaging helps to prevent others from tampering with a company's product.

Terms

Acceptable Quality Limit (AQL): an inspection of components or filled vials/syringes to both determine the number and types of defects and evaluate them against a predetermined numerical value that represents the maximum number of each level of defect that can be found during QA inspection without impacting overall batch quality

Adequate directions for use: directions under which the layman can use a drug both safely and for the purposes for which it is intended

Clinical trials

- **Open label trials:** trials in which both researchers and participants are aware of which treatment is being administered; for these trials, vials and syringes can have labels that directly identify the compound and dosage.
- **Single blind trials:** trials in which those administering the drug are aware of whether the treatment is active or placebo but the patient is unaware; the vials and syringes can be labeled with a code or lot number that makes it directly evident to the physician which compound is being administered.
- **Double blind trials:** both the administrators and the participants are unaware of which treatment is being administered; labeling strategies must be implemented so that the contents of the vial/syringe are not known by the physician administering the drug; however, later identification by the company conducting the trial is possible.

Container closure system: refers to the sum of packaging components that together contain and protect the dosage form; this includes both primary packaging components and secondary packaging components if the latter are intended to provide additional protection to the drug product; a *packaging system* is equivalent to a container closure system.

Inspection

- **Automated Inspection:** fully automated inspection systems involve multiple camera systems for inspecting large numbers of product containers at a high rate of speed
- **Manual Inspection:** an inspection of components or filled vials/syringes performed by an operator who picks up and exams items per predefined formal inspection procedures and AQL specifications; filled vials and syringes are usually examined in a light booth against both white and dark backgrounds.
- **Semi-Automated Inspection:** a manual inspection combining inspection by personnel with an integrated conveyor and timing system

Labeling: per 21 CFR § 201(m) labeling is "all labels and other written, printed, or graphic matter…

1) upon any article or any of its containers or wrappers or
2) accompanying such article at any time while a device is held for sale after shipment or delivery for shipment in interstate commerce."

Packaging (source**:** FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics, May 1999—examples and images of types of packaging are provided later in this chapter).

Materials of construction: refers to the substances (e.g., glass, high density polyethylene [HDPE] resin, metal) used to manufacture a packaging component.

Packaging component: any single part of a container closure system; typical components are containers (e.g., ampoules, vials, bottles), container liners (e.g., tube liners), closures (e.g., screw caps, stoppers), closure liners, stopper overseals, container inner seals, administration ports (e.g., on large-volume parenterals [LVPs]), overwraps, administration accessories, and container labels.

Primary packaging component: a packaging component that either is or may be in direct contact with the dosage form

Secondary packaging component: a packaging component that is not and will not be in direct contact with the dosage form

Inspection

In addition to meeting chemical and microbiological specifications, parenteral products must be visually inspected for defined attributes. Each container produced during a manufacturing run must be examined for both container defects and product defects. Defects are categorized based both on the likelihood of the defect being found in inspection and the potential impact of the defect if it is not discovered during the inspection process. Using these criteria, they are classified as critical, major and minor defects. Once trained manufacturing personnel have inspected the batch, Quality Assurance (QA) personnel perform an additional check. Based on batch size, a statistical sample is pulled and inspected by QA. This inspection is referred to as Acceptable Quality Limit (AQL). Each of the defect categories is assigned a numerical value that represents the maximum number of each level of defect that can be found during QA inspection without impacting overall batch quality. The American National Standards Institute/American Society for Quality Control (ANSI/ASQC) Z1.4-2008, *Sampling Procedures and Tables for Inspection by Attributes* is the primary reference used for setting AQL levels.

Table 15-1. Sample AQL table based on ANSI/ASQC, Z1.4-2008

Batch Size	Sample Size	Allowable Critical Defects 0.065%	Allowable Major Defects 1.0%	Allowable Minor Defects 2.5%
501-1,200	200	0	5	10
1,201-3,200	200	0	5	10
3,201-10,000	200	0	5	10
10,001-35,000	315	0	7	14
35,001-150,000	800	1	14	21
150,001-500,000	800	1	14	21
500,001 and over	1250	2	21	21

Manual inspection

With manual inspection, an inspector physically picks up and examines the drug product containers. The manual inspection process employs the use of a lighted booth (Figure 15-1) with a back wall composed of non-glare material that is divided into two halves—one black and one white. The inspector picks up one or more containers, depending on the size, and examines the container(s) in the lighted booth once in front of the black background and once in front of the white background. Various defects will at times be more apparent when viewed against one color versus the other.

Figure 15-1. Pharmaceutical manual inspection booth (courtesy OEM-Optical)

The amount of time each container or set of containers is inspected should be limited and defined within the inspection Standard Operating Procedure (SOP). Prolonged examination does not result in a better inspection; it generally results in a high level of false rejects. Any containers having identified defects are rejected. Each defect is recorded in the appropriate category (critical, major, or minor), and at the end of the inspection the number of rejects is totaled. Limits for each defect type or overall defect limits are individual to each manufacturer. Some have in-process limits that may trigger a tighter AQL (a larger sample set will be taken for the AQL inspection). Others have limits for percentage of defects that may trigger an investigation if exceeded. In summary there is a mechanism in place to recognize and react to out-of-trend results that may impact product quality.

Semi-automated inspection

Semi-automated inspection is a manual inspection with an integrated conveyor and timing system. There are generally several booths linked together (Figure 15-2), and the vials are delivered to the inspectors by the conveyor. The vials travel down the conveyor and stop for the set inspection time. The inspector picks up the vials, performs the inspection in the lighted booth, and places the vials back onto the conveyer to proceed to traying off. This procedure can increase efficiency, as the inspectors do not have to handle a single tray at a time, and the amount of time spent inspecting each container/set of containers is more tightly controlled. Another advantage is that these systems generally include automated counting, so at the end of the process the inspectors do not have to count the units inspected.

Figure 15-2. Pharmaceutical semi-automatic inspection booth (courtesy Dabrico, Inc.)

Automated inspection

Fully automated inspection systems (Figures 15-3 and 15-4) involve multiple camera systems for inspecting large numbers of product containers at a high rate of speed. These systems are far more expensive and require extensive testing and validation before they can be used in manufacturing processes; however, they are more efficient and effective, especially in the case of larger batch sizes that number hundreds of thousands of units.

Figure 15-3. Automated vial inspection machine (courtesy Bosch Packaging Technology)

Figure 15-4. Automated syringe inspection using optical sensor to detect particulates (courtesy Eisai Machinery and Bosch Packaging Technology)

Labeling

Labeling of all drug products is required in order to both provide accurate information regarding the product and avoid misrepresentation of the ingredients or effects of a drug, whether accidental or intentional. Each separate product, including different strengths or concentrations of the same API, must be separately labeled and identified. Labels can be applied directly to the primary container; included as a package insert; or applied to secondary packaging materials, such as a bulk pack box.

Label printing and handling must be carefully monitored at all steps during the process. All labeling materials, such as blank labels and labeling equipment, must be tested beforehand to ensure that they operate correctly and fit any specific requirements for the type of labeling that will be applied to the product. The information to be included on the label is established as part of the regulatory submission; must adhere to FDA requirements; and must be verified for correctness. Special precautions must be taken at all times to avoid mislabeling. Any leftover labels from a designated batch should be discarded to avoid accidentally using these labels on incorrect batches. If there is ever any doubt whether or not to apply a label to a certain product, the label should not be used and a supervisor or Quality Assurance representative should be contacted for instruction on how to proceed.

Labeling machinery

In some cases it is preferred to manually print and apply labels to bottles, drug product primary containers, or bulk packages. However, there is a variety of labeling machines currently employed in pharmaceutical manufacturing and other industries. These machines can be used to label individual vials, bottles, and syringes, as well as bulk packages. Some machines print and apply the labels while others just apply the label and require the operator to feed labels into the machine.

Labeling equipment is generally classified as either semi-automatic (Figure 15-5) or fully automatic (Figure 15-6). Semi-automatic labeling machines require some manual processing by the machine operator (e.g., placing the vial into position in the machine). No change parts are

required for different sized containers, and these machines are relatively simple and effective for labeling round containers, even if the containers are grooved or notched. Automatic labeling machines are fully automated in that they position the containers and then apply the labels.

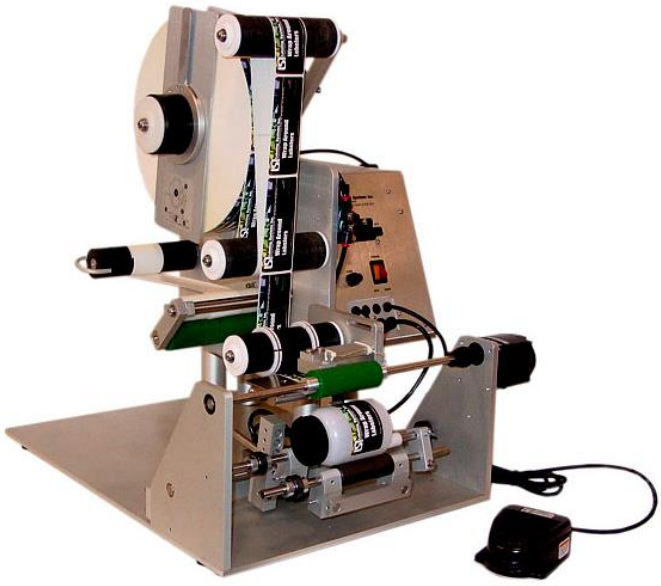


Figure 15-5. Semi-automatic labeling machine (courtesy Professional Packaging Systems)

Figure 15-6. Automatic vial sticker labeling machine (courtesy GMPMax)

Videos of labeling machines in operation:
http://www.labelingsystems.com/videos/semi-automatic-wrap-label-applicator/

The remainder of this section contains a list of some of the many regulations and guidelines that the FDA has in place regarding label control. These regulations govern all labeling activities, including manufacturing processes; materials permissible for use; printing, application, and disposal practices; and label design and recommendations related to font sizes and colors.

FDA regulations

FDA 21 CFR Parts 210 & 211 (Revised as of April 1, 2013)

21 CFR § 201(k) defines "label" as a:

- "display of written, printed, or graphic matter upon the immediate container of any article..."

  The term "immediate container" does not include package liners. Any word, statement, or other information appearing on the immediate container must also appear "on the outside container or wrapper, if any there be, of the retain package of such article, or is easily legible through the outside container of wrapper."

21 CFR § 201(m) defines "labeling" as:

- "all labels and other written, printed, or graphic matter
  a) upon any article or any of its containers or wrappers or

b) accompanying such article at any time while a device is held for sale after shipment or delivery for shipment in interstate commerce."

The term "accompanying" is interpreted liberally to mean more than physical association with the product. It extends to association through methods that include posters, tags, pamphlets, circulars, booklets, brochures, instruction books, direction sheets, and fillers. "Accompanying" also includes labeling that is brought together with the device after shipment or delivery for shipment in interstate commerce.

FDA regulations regarding "adequate directions for use":

- "Adequate directions for use" means directions under which the layman can use a drug both safely and for the purposes for which it is intended (21 CFR § 201.128 defines "intended use"). Directions for use may be inadequate due to, among other reasons, omission, in whole or in part, or incorrect specification of:
    a) statements of all conditions, purposes, or uses for which such drug is intended, including conditions, purposes, or uses for which it is prescribed, recommended, or suggested in its oral, written, printed, or graphic advertising, and conditions, purposes, or uses for which the drug is commonly used; except that such statements shall not refer to conditions, uses, or purposes for which the drug can be safely used only under the supervision of a practitioner licensed by law and for which it is advertised solely to such practitioner.
    b) quantity of dose, including usual quantities for each of the uses for which it is intended and usual quantities for persons of different ages and different physical conditions.
    c) frequency of administration or application.
    d) duration of administration or application.
    e) time of administration or application (in relation to time of meals, time of onset of symptoms, or other time factors).
    f) route or method of administration or application.
    g) preparation for use (e.g., shaking, dilution, adjustment of temperature, or other manipulation or process).

FDA regulations regarding "misleading statements":

- 21 CFR § 201.6 Drugs; misleading statements:

    a) Among representations in the labeling of a drug which render such drug misbranded is a false or misleading representation with respect to another drug or a device or a food or cosmetic.
    b) The labeling of a drug which contains two or more ingredients may be misleading by reason, among other reasons, of the designation of such drug in such labeling by a name which includes or suggests the name of one or more but not all such ingredients, even though the names of all such ingredients are stated elsewhere in the labeling.

Regulatory requirements regarding labeling operations in drug product manufacturing:

Part 211 – Current Good Manufacturing Practice for Finished Pharmaceuticals
Subpart G – Packaging and Labeling Control

- § 211.122 Material examination and usage criteria:

    a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials; such written procedures shall be followed. Labeling and packaging materials shall be representatively sampled and examined or tested upon receipt and before use in packaging or labeling of a drug product.
    b) Any labeling or packaging materials meeting appropriate written specifications may be approved and released for use. Any labeling or packaging materials that do not meet such specifications shall be rejected to prevent their use in operations for which they are unsuitable.
    c) Records shall be maintained for each shipment received of each different labeling and packaging material indicating receipt, examination or testing, and whether accepted or rejected.
    d) Labels and other labeling materials for each different drug product, strength, dosage form, or quantity of contents shall be stored separately with suitable identification. Access to the storage area shall be limited to authorized personnel.
    e) Obsolete and outdated labels, labeling, and other packaging materials shall be destroyed.

    Use of gang-printed labeling for different drug products, or different strengths or net contents of the same drug product, is prohibited unless the labeling from gang-printed sheets is adequately differentiated by size, shape, or color.

    If cut labeling is used, packaging and labeling operations shall include one of the following special control procedures:

        1. dedication of labeling and packaging lines to each different strength of each different drug product
        2. use of appropriate electronic or electromechanical equipment to conduct a 100 percent examination for correct labeling during or after completion of finishing operations for hand-applied labeling; such examination shall be performed by one person and independently verified by a second person.
        3. use of visual inspection to conduct a 100 percent examination for correct labeling during or after completion of finishing operations for hand-applied labeling; such examination shall be performed by one person and independently verified by a second person.

4. use of any automated technique, including differentiation by labeling size and shape, that physically prevents incorrect labeling from being processed by labeling and packaging equipment

f) Printing devices on or associated with, manufacturing lines used to imprint labeling upon the drug product unit label or case shall be monitored to assure that all imprinting conforms to the print specified in the batch production record.

- § 211.125 Labeling issuance

a) Strict control shall be exercised over labeling issuance 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).
d) All excess labeling bearing lot or control numbers shall be destroyed.
e) Returned labeling shall be maintained and stored in a manner to both prevent mix-ups and provide proper identification.
f) Procedures shall be written describing in sufficient detail the control procedures employed for the issuance of labeling; such written procedures shall be followed.

- § 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 mix-ups 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 inspections shall be documented in the batch production records.

- § 211.134 Drug product inspection

    a) Packaged and labeled products shall be examined during finishing operations to provide assurance that containers and packages in the lot have the correct label.
    b) A representative sample of units shall be collected at the completion of finishing operations and shall be visually examined for correct labeling.
    c) Results of these examinations shall be recorded in the batch production or control records.

Labeling for clinical trials

There are three typical types of clinical trials:

- open label trials: trials in which both researchers and participants are aware of which treatment is being administered; for these trials, vials and syringes can have labels that directly identify the compound and dosage.
- single blind trials: trials in which those administering the drug are aware of whether the treatment is active or placebo but the patient is unaware; the vials and syringes can be labeled with a code or lot number that makes it directly evident to the physician which compound is being administered.
- double blind trials: both the administrators and the participants are unaware of which treatment is being administered; labeling strategies must be implemented so that the contents of the vial/syringe are not known by the physician administering the drug; however, later identification by the company conducting the trial is possible.

When labeling a drug that is being used in clinical trials, the FDA requires the product to be labeled as such—described below in part 312 of the Investigational New Drug Application.

- Subpart A--General Provisions - §312.6 Labeling of an investigational new drug

    a) The immediate package of an investigational new drug intended for human use shall bear a label with the statement "Caution: New Drug--—Limited by Federal law (or (United States) law to investigational use."
    b) The label or labeling of an investigational new drug shall not bear any statement that is false or misleading in any particular and shall not represent that the investigational new drug is safe or effective for the purposes for which it is being investigated.

c) The appropriate FDA Center Director, according to the procedures set forth in § 201.26 or § 610.68 of this chapter, may grant an exception or alternative to the provision in paragraph (a) of this section, to the extent that this provision is not explicitly required by statute, for specified lots, batches, or other units of a human drug product that is or will be included in the Strategic National Stockpile.

Manufacturer

For Clinical Trial Use Only

Drug Name, X mg/mL, Y mL/vial

Store refrigerated 2–8 °C (36–46 °F)

Product Code: XXXXXX

Lot No: XXXXX

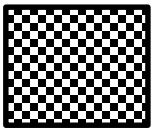
Case ____ of _____

Quantity _____ vials

Caution: New Drug—Limited by Federal law (USA) to investigational use.

Sponsor: Company
Company's Address

Made in USA



<- QR Code LBL-XXX-XXX-XXX

Figure 15-7. Example of a manufacturing label for a case of vials intended for clinical trial use

Commercial labels

Every pharmaceutical preparation must comply with the labeling requirements established under GMP (Figures 15-8 and 15-9). The label should include:

- the name of the pharmaceutical product
- the name(s) of the active ingredient(s); International Nonproprietary Names (INN) should be used wherever possible

- the amount of the active ingredient(s) in a suitable dose volume and the volume in the container; for powder for injections: the amount of the active ingredient(s) in the container and a statement of the net contents (e.g., number of dosage units)
- the batch number assigned by the manufacturer
- the expiry date and, when required, the date of manufacture
- any special storage conditions or handling precautions that may be necessary
- directions for use and warnings and precautions that may be necessary (e.g., that the product must be used in conjunction with a final filter)
- the name and address of either the manufacturer or the person responsible for placing the product on the market
- information on any added antimicrobial preservative where applicable

Source: *The International Pharmacopoeia Fifth Edition 2015*

For parenteral preparations that are solutions or dispersions, the concentration of the active ingredient(s) should be given in terms of mass or biological activity per volume. For concentrated solutions, labels should state both the composition and the dilution to be carried out before use.

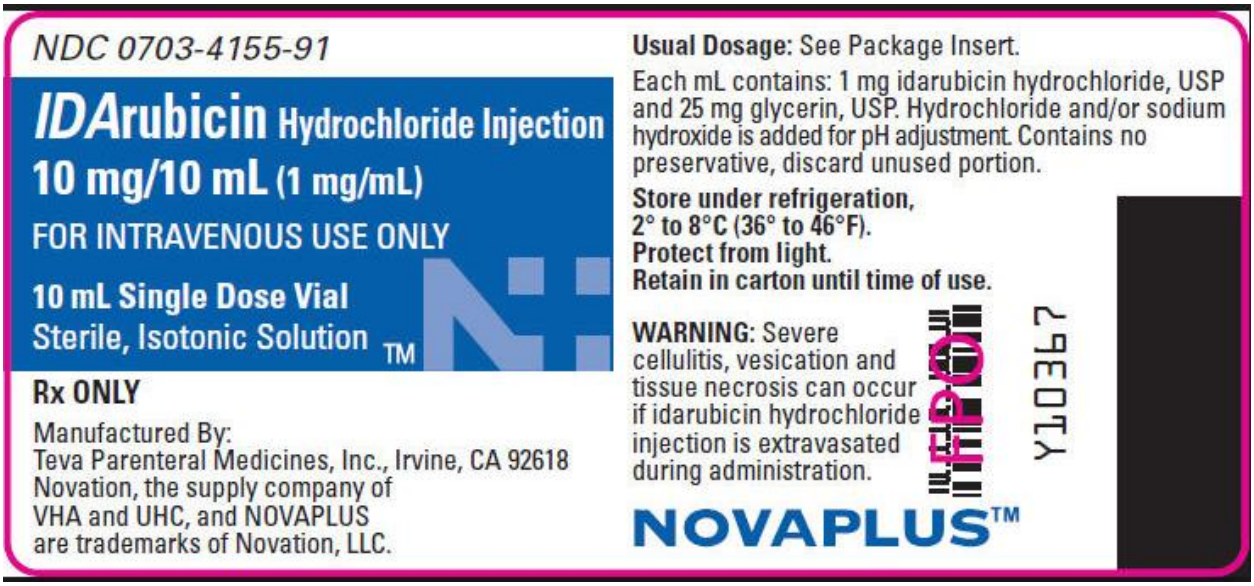


Figure 15-8. Example of a commercial parenteral drug label (the expiry listed on this label is a code rather than the guideline recommended format of MMMYYYY)

Figure 15-9. Example of a commercial label on a tray pack containing four pre-filled syringes

FDA Non-binding guidelines and recommendations for label design

Principal display panel: the part of a label that is most likely to be displayed, presented, shown, or examined under customary conditions of display on the pharmacy or retail shelf—should contain:

- proprietary name
- established name/proper name
- product strength
- route of administration

- warnings
- any other information included on the principal display panel (e.g., manufacturer name or "Rx-only")—should not compete in size and prominence with the important information listed above

Text Size and Style

- Font should be easy to read and not lightweight or condensed.
- A number of published references recommend a larger font size, such as 12-point *sans serif* (e.g., *Arial*).
- FDA recommends the use of at least a 12-point font when label size permits.

  Tall man lettering: dissimilar letters in different established names are placed in uppercase letters to aid in differentiation between the two (e.g., **acetaZOLAMIDE vs. acetoHEXAMIDE**)

Color Differentiation

- Products should be differentiated within a manufacturer's product line.
- Strengths should be differentiated within a manufacturer's product line.
- Certain aspects of the label, especially warning information, should be highlighted.
- Color-coding:
  a) FDA generally recommends avoiding color-coding in most instances.
  b) Color-coding is reserved for special circumstances and only after human factors testing and feedback on the prototype from all end users is received and evaluated by FDA prior to use.
  c) Only a few applications of color-coding are appropriate (e.g., caps for ophthalmic products to distinguish therapeutic class).

Confusing Abbreviations

- Certain abbreviations, acronyms, and symbols are dangerous and should be avoided, as they can be misinterpreted and lead to errors that result in patient harm.
- Mistakes can also result from the use of abbreviations, symbols, and dose designations whose meanings are non-standardized and/or unfamiliar to the healthcare professional or other target reader.

Clear Container Labels

- Text that is raised or recessed on clear, transparent, or translucent containers (e.g., LDPE vials) is generally illegible.
- The product should be wrapped so that a legible label is applied to the overwrap; the product should remain in the overwrap until it is administered.

Product Strength

- Product strength should be explicit.
- The unit of measure used should be consistent throughout.
- For small volume parenteral drugs, the total quantity per total volume should be listed, followed by the concentration—500 mg / 10 mL (50 mg/mL).
- If the total volume > 1 mL, a concentration value SHOULD NOT BE LISTED in mg/Ml.

Expiration Date

- The recommended format, rather than using obscure abbreviations, is: MMMYYYY or MMMDDYYYY.

National Drug Code Numbers

- Each drug product is assigned a unique 10-digit, 3-segment number; when this number is displayed on the label it must be clearly differentiated from other products of different strength, or different drugs produced by the same manufacturer, to avoid possible confusion.

Transferrable Labels

- Once an injectable drug is withdrawn from the commercial vial into a syringe for administration, the syringe no longer provides crucial information to the end user.
- When possible, transferrable or peel-off labels should be used that can be applied to the syringe to minimize the use of unlabeled syringes.

QR Codes

- The FDA has not yet developed a formal position on the use of QR codes.
- It is recommended that they appear on the side or back panel of the container label or carton labeling.
- QR codes should neither compete with nor distract from the presentation of important information.

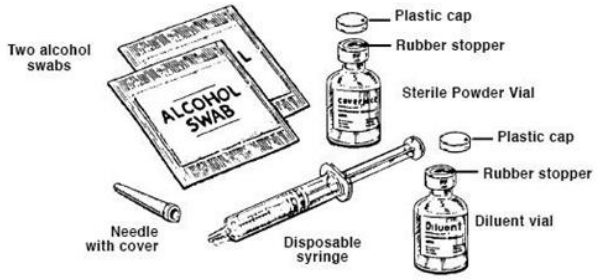
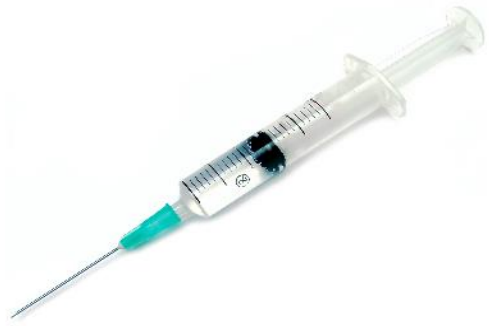
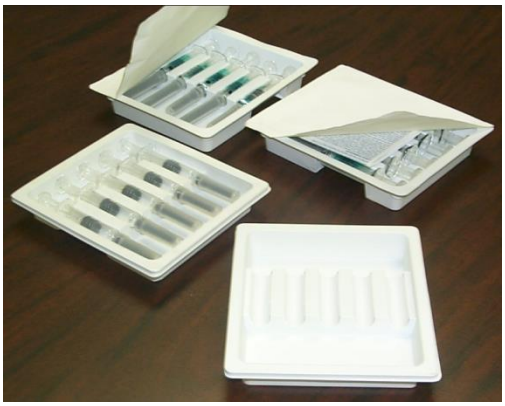
Full document available at:
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

Packaging

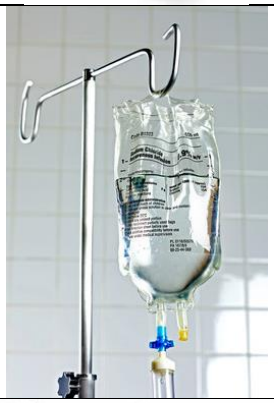
Secondary packaging includes any packing or labeling materials that are not directly in contact with the product. This includes any syringe accessories (e.g., plunger rods or safety devices), as well as what is traditionally considered a package, such as cartons or bulk packs. Secondary packaging is an important aspect of keeping the product safe from damage or tampering. Vials and syringes are protected from breakage when encased in cartons, blister packs, or trays.

Table 15-2 provides descriptions of some common forms of packaging, both primary and secondary, and their official FDA definitions.

Table 15-2. Description of common primary and secondary packaging types for parenteral pharmaceuticals

Packaging Type	Description	Example
Package	the drug product container with any accompanying materials or components; this may include the protective packaging, labeling, and administration devices.	
Syringe	a device for the administration of parenteral drug products that consists of a rigid barrel fitted with septum with a plunger at one end and a seal or needle at the other end: the needle assembly may be either part of the device or separate.	
Tray	a shallow, flat receptacle with a raised edge or rim used for carrying, holding, or displaying finished drug product in its primary or market package; a tray and its contents may be either encased in shrink-wrapped plastic for shipping or covered or overwrapped as part of a unit-of-use package or kit.	

Packaging Type	Description	Example
Blister Pack	a package that consists of molded plastic or laminates that has indentations (viewed as blisters when flipped) into which a dosage form is placed; a covering, usually of laminated material, is then sealed to the molded part.	
Vial	a container designed for use with parenteral drug products: • single-dose: a vial containing a single unit of a parenteral drug product • single-use: a vial from which a single dose of a parenteral drug product can be removed—the vial and its remaining contents can be discarded..	
Pharmacy Bulk Package (Vial)	a container of a sterile preparation whose contents are intended for use in a pharmacy admixture program; used for the filling of empty sterile syringes; must be prominently labeled as “Not for Direct Infusion”	

Packaging Type	Description	Example
Piggyback Vial	a vial that contains a parenteral preparation that can be attached directly to the tubing of a parenterally administered fluid	
Bag	A sac or pouch usually used for the administration or storage of sterile parenteral/IV drugs	
Ampoule	a container capable of being hermetically sealed and intended to hold sterile materials	
Bottle	a vessel with a narrow neck designed to accept a specific closure: • applicator • dispenser • dropper • glass • plastic • pump • spray • unit-dose	

Packaging Type	Description	Example
Dewar	a container usually composed of glass or metal that has at least two walls with the space between each wall evacuated so as to prevent the transfer of heat; the inside of the container often has a coating (as silvering) on the inside to reduce heat transfer and is used especially for storing liquefied gases or for experiments at low temperatures.	
Packet	an envelope into which only one dose of a drug product, usually in the form of granules or powder, has been directly placed	

For more package types and their definitions:
http://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/datastandardsmanualmonographs/ucm071748.htm

All packaging materials, whether primary or secondary, must show suitability for their intended use:

> "Every proposed packaging system should be shown to be *suitable* for its intended use: it should adequately *protect* the dosage form; it should be *compatible* with the dosage form; and it should be composed of materials that are considered *safe* for use with the dosage form and the route of administration."
> *FDA Guidance for Industry III.B.1*

Secondary packaging components are identified by the FDA as serving one or more of the following functions:

a) provide protection from excessive transmission of moisture or solvents into or out of the packaging system

b) provide protection from excessive transmission of reactive gases (atmospheric oxygen, inert headspace filler gas, or other organic vapors) into or out of the packaging system
c) provide light protection for the packaging system
d) provide protection for a packaging system that is flexible or needs extra protection from rough handling
e) provide an additional measure of microbiological protection (e.g., by maintaining sterility or by protecting the packaging system from microbial intrusion)

Since secondary packaging components are not intended to make contact with the dosage form of the drug product, they are regulated somewhat differently than primary container closure components. In a new drug application, emphasis is typically placed on the primary components, and only a brief description of the secondary packaging method is usually required. There is generally less concern regarding the materials of construction of secondary packaging materials, whereas for a primary component, it is crucial to be aware of the potential for leachables and extractables that could negatively interact with the product. If the secondary packaging component is specifically intended to provide extra safety measures to the product, such as a safety device attached to a syringe, complete information about the packaging material should be provided, including proof that the packaging actually accomplishes the added safety benefits. Additionally, if the secondary packaging material is quite permeable, such as low density polyethylene (LDPE), the packaging could be considered a potential source of contamination. Permeable packaging materials, in some cases, can facilitate migration of ink or adhesive materials, which can harm the drug product.

The FDA has specific guidelines regarding the use of childproof packaging—"Special packaging is defined as packaging that is designed or constructed to be significantly difficult for children under 5 years of age to open or obtain a toxic or harmful amount of the substance contained therein within a reasonable time and not difficult for normal adults to use properly, but does not mean packaging which all such children cannot open or obtain a toxic or harmful amount within a reasonable time." Special packaging is generally required for both reclosable and unit-dose (not reclosable) packaging systems. Situations when special packaging is not a manufacturing requirement include: when a prescription drug will be repackaged by a pharmacist; delivered to a physician or other prescribing practitioner; or dispensed for use in an institution such as a hospital or nursing home.

Packaging that is tamper-evident has an indicator or barrier to entry that if breached or missing can be reasonably expected to provide visual or audible evidence to the consumer that tampering has occurred (Figure 15-10). Currently, the FDA has strict mandates regarding tamper-evident packaging for over-the-counter (OTC) pharmaceuticals (21 CFR Part 11: 211.132); however, parenteral manufacturers typically incorporate tamper-evident packaging as well. Vials use caps or seals to secure the rubber stopper in the container. These seals are usually equipped with a plastic top that cannot be repositioned once removed. When syringes are packaged in blister packs or trays, the packaging is designed so that it is immediately apparent if the blister or film has been breached. In some cases, labels can also be applied in such a way that it is evident whether or not either the product or the label itself has been tampered with.

Figure 15-10. Examples of tamper-evident packaging in parenteral pharmaceuticals (left to right: syringe caps, flip-off vial seals, tamper-evident labeling)

A useful resource for additional packaging recommendations:

World Health Organization
Annex 9—Guidelines on packaging for pharmaceutical products:
http://www.who.int/medicines/areas/quality_safety/quality_assurance/GuidelinesPackagingPharmaceuticalProductsTRS902Annex9.pdf

Automated secondary packaging

Some packaging materials can be assembled manually; for example, an operator can either assemble syringes with plungers and place the syringes into a tray or pack vials into a bulk package. However, particularly for large batch sizes, it is more efficient and effective to utilize packaging machinery. High-speed assembly machines can be utilized to assemble accessories for prefilled syringes. Some of these machines can also be used to apply labels to the individual syringes (Figure 15-11).

Figure 15-11. High-speed syringe assembly (courtesy DWFritz)

Automated syringe blister packaging machines allow syringes to be fed onto an assembly line and evenly spaced out (Figure 15-12). The machine places the syringes into plastic preformed blister trays. The cover film is then applied to the top of the blister pack and sealed. Some blister packaging machines are also equipped with the ability to apply labels to the blisters or the film cover. Tray pack machines function in a similar way—syringes are loaded and separated to be placed in the plastic trays (Figure 15-12). A film is then applied over the tray to seal the syringes inside. Alternatively the tray can be packaged into a plastic or cardboard carton, which can then be labeled.

Figure 15-12. Left: internal view of a blister packaging machine (courtesy Greathealth Trexim)
Right: tray pack thermoforming machine (courtesy MG America)

Check Your Knowledge

1. Defects are categorized based upon:
   a. the number of the same types of defects
   b. the likelihood of the defect being found in inspection
   c. the potential risk/impact of the defect if it is not discovered during inspection
   d. answers b and c
2. AQL represents:
   a. the maximum number of each level of defect that can be found during QA inspection without impacting overall batch quality
   b. American Quality League
   c. the number of major and null defects found in a batch
   d. the number of critical and secondary defects found in a batch
3. The term "labeling" refers to printed, written, and graphic material:
   a. on the primary container of the drug product
   b. on secondary containers and wrapping
   c. on printed, written, and graphic material accompanying the drug product (e.g., posters, tags, pamphlets, circulars, booklets, brochures, instruction books, direction sheets, and fillers)
   d. all of the above
4. List at least three things that must be included in "adequate directions for use."

   _____

   _____

   _____

5. Obsolete labels, labeling, and packaging that include lot or control numbers must be:
   a. kept in a clean, dry, secure room for use with the next batch
   b. destroyed in a controlled, documented manner
   c. attached to the batch record
   d. none of the above
6. A clinical trial in which the administrator knows whether the drug is the actual drug or a placebo but the patient does not is known as a:
   a. double blind trial
   b. blind trial
   c. open label trial
   d. physician-centric trial

7. Examples of “misleading statements” that are prohibited from being used in labeling include:
   a. unsubstantiated comparisons /connections to other drugs
   b. suggestions that the drug contains only one ingredient when it actually contains several
   c. answers a and b
   d. attempts to use inappropriate humor, irony, or sarcasm
8. Secondary packaging is often designed to protect against:
   a. rough handling
   b. light and/or microbial intrusion
   c. excessive transmission of moisture or reactive gases
   d. all of the above