

## BRIEFING

**< 7 > Labeling.** This general chapter provides definitions and standards for labeling of official articles. Note that, as with compendial quality standards, labeling requirements also may be enforceable under law. In the United States, to avoid being deemed misbranded, drugs recognized in *USP–NF* must be packaged and labeled in compliance with compendial standards [see the Food, Drug, and Cosmetic Act (FDCA) sections 501(b), 502(e)(3)(b), 502(g), and 21 *Code of Federal Regulations* 299.5]. FDCA also recognizes compendial (*USP–NF*) packing and labeling standards for “deteriorative drugs” [502(h)].

The Expert Committee proposes relocating all labeling requirements from the *Preservation, Packaging, Storage, and Labeling* section in the *General Notices* and general chapter *Injections* **< 1 >** to create this new chapter. The labeling standards for ferrules and cap overseals in this chapter have not changed and will become official on December 1, 2013. Many monographs have unique labeling requirements that should be used consistently.

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*Comment deadline:* March 31, 2012

### **Add the following:**

## **▲ < 7 > LABELING**

### **DEFINITION**

The term *labeling* designates all labels and other written, printed, or graphic matter on an article's immediate container or on or in any package or wrapper in which it is enclosed, except any outer shipping container. The term *label* designates that part of the labeling on the immediate container.

A shipping container that contains a single article, unless the container also is essentially the immediate container or the outside of the consumer package, must be labeled with a minimum of product identification (except for controlled articles), lot number, expiration date, and conditions for storage and distribution.

In addition to compendial requirements, articles in *USP–NF* also are subject to compliance with more comprehensive labeling requirements promulgated by governmental bodies.

### **LABELS AND LABELING**

The label states the following information:

- name of the preparation
- in the case of a liquid preparation, the percentage content of drug or amount of drug in a specified volume
- in the case of a dry preparation, the amount of active ingredient
- the route of administration
- a statement of storage conditions and an expiration date
- the name and place of business of the manufacturer, packer, or distributor
- an identifying lot number.

The lot number must be traceable to the complete manufacturing history of the specific package, including all manufacturing, filling, sterilizing, and labeling operations.

If the individual monograph permits varying concentrations of active ingredients in a large-volume parenteral (LVP), the concentration of each ingredient named in the official title is stated as if it were part of the official title, e.g., *Dextrose Injection 5%*, or *Dextrose (5%) and Sodium Chloride (0.2%) Injection*.

If the complete formula is not specified in the individual monograph, the labeling includes the following information: (1) In the case of a liquid preparation, the percentage content of each ingredient or the amount of each ingredient in a specified volume, except that ingredients added to adjust to a given pH or to make the solution isotonic may be declared by name and a statement of their effect; and (2) in the case of a dry preparation or other preparation to which a diluent must be added before use, the amount of each ingredient, the composition of recommended diluent(s) [the name(s) alone if the formula is specified in the individual monograph], the amount that will be used to attain a specific concentration of active ingredient, the final volume of solution, a brief description of the physical appearance of the constituted solution, directions for proper storage of the constituted solution, and an expiration or beyond-use date (see *Expiration Date and Beyond-use Date* below).

Containers for injections that are intended for use as dialysis, hemofiltration, or irrigation solutions and that contain a volume of more than 1 L should be labeled to indicate that the contents are not intended for use by intravenous infusion.

Injections that are intended for veterinary use should be labeled to that effect.

The container shall be labeled so that a sufficient area of the container remains uncovered for its full length or circumference to permit inspection of the contents.

#### **Amount of Ingredient per Dosage Unit**

The strength of a drug product is expressed on the container label in terms of micrograms or milligrams or grams or percentage of the therapeutically active moiety or drug substance, whichever form is used in the title, unless otherwise indicated in an individual monograph. Both the active moiety and drug substance names and their equivalent amounts then are provided in the labeling.

Official articles in capsule, tablet, or other dosage forms shall be labeled to express the quantity of each active ingredient or recognized nutrient contained in each unit. An exception involves unit-dose oral solutions or suspensions (whether supplied as liquid preparations or as liquid preparations that are constituted from solids upon addition of a designated volume of a specific diluent). For these products the label shall express the quantity of each active ingredient or recognized nutrient delivered under the conditions prescribed in *Deliverable Volume* ( 698 ). Official drug products not in unit dosage form shall be labeled to show the quantity of each active ingredient in each milliliter or in each gram or to express the percentage of each such ingredient (see *General Notices 8.140, Percentage Concentrations*). Exceptions are oral liquids or solids intended to be constituted to yield oral liquids that, alternatively, can be labeled in terms of each 5-mL portion of the liquid or resulting liquid. Unless otherwise indicated in a monograph or chapter, declarations of strength or quantity shall be stated only in metric units. See also *General Notices 5.50.10, Units of Potency (Biological)*.

### **Expiration Date and Beyond-use Date**

The label of an official drug product or nutritional or dietary supplement product shall bear an expiration date. All products shall display the expiration date so that it can be read by an ordinary individual under customary conditions of purchase and use. The expiration date shall be prominently displayed in high contrast to the background, or it shall be sharply embossed and easily understood (e.g., “EXP 6/12,” “Exp. June 12,” or “Expires 6/12”). The monographs for some preparations state how the labeled expiration date shall be determined. In the absence of a specific requirement in the individual monograph for a drug product or nutritional supplement, the label shall bear an expiration date assigned for the particular formulation and package of the product, with the following exceptions: the label need not show an expiration date if the drug product or nutritional supplement is packaged in a container that is intended for sale without prescription, if the labeling states no dosage limitations, and if the product or supplement is stable for not less than 3 years when stored under the prescribed conditions.

If an official product is required to bear an expiration date, the product shall be dispensed solely in or from a container labeled with an expiration date, and the date on which the article

is dispensed shall be within the labeled expiry period. The expiration date identifies the time during which the article can be expected to meet the requirements of the compendial monograph, provided it is kept under the prescribed storage conditions. The expiration date limits the time during which the article may be dispensed or used. If an expiration date is stated only in terms of the month and the year, then the intended expiration date is the last day of the stated month. The beyond-use date is the date after which a product shall not be used. The dispenser shall place on the label of the prescription container a suitable beyond-use date to limit the patient's use of the article based on any information supplied by the manufacturer. The beyond-use date shall not be later than the expiration date on the manufacturer's container.

For articles that require constitution before use, a suitable beyond-use date for the constituted product shall be identified in the labeling.

For all other dosage forms, in determining a beyond-use date the dispenser shall take into account, in addition to any other relevant factors:

- the nature of the drug
- the container in which it was packaged by the manufacturer and the expiration date thereon
- the characteristics of the patient's container, if the article is repackaged for dispensing
- the expected storage conditions to which the article may be exposed
- any unusual storage conditions to which the article may be exposed
- the expected length of the course of therapy.

After considering these factors, the dispenser shall label a container with a suitable beyond-use date to limit the patient's use of the article. Unless otherwise specified in the individual monograph or in the absence of stability data to the contrary, the beyond-use date shall be not later than (a) the expiration date on the manufacturer's container, or (b) 1 year from the date the drug is dispensed, whichever is earlier. For nonsterile solid and liquid dosage forms that are packaged in single-unit and unit-dose containers, the beyond-use date shall be 1 year from the date the drug is packaged into the single-unit or unit-dose container or the expiration date on the manufacturer's container, whichever is earlier, unless stability data or the manufacturer's labeling indicates otherwise.

The dispenser shall maintain packaging and storage facilities at a mean kinetic temperature not greater than 25°. The plastic material used in packaging the dosage forms shall afford better protection than polyvinyl chloride, which does not adequately protect against moisture permeation. Dispensers shall keep records of the temperature of the facility where the dosage forms are stored and of the plastic materials used in packaging.

STRENGTH AND TOTAL VOLUME FOR SINGLE- AND MULTIPLE-DOSE INJECTABLE DRUG PRODUCTS

For single- and multiple-dose injectable drug products, the strength per total volume should be the primary and prominent expression on the principal display panel of the label, followed in close proximity by strength per mL enclosed by parentheses. For containers that hold a volume of less than 1 mL, the strength per fraction of a mL should be the only expression of strength. Strength per single mL should be expressed as mg/mL, not mg/1 mL.

The following formats are acceptable for contents of greater than 1 mL:

total strength/total volume: 500 mg/10 mL

strength/mL: 50 mg/mL

or

total strength/total volume: 25,000 Units/5 mL

strength/mL: 5000 Units/mL.

The following format is acceptable for contents of less than 1 mL: 12.5 mg/0.625 mL.

There are some exceptions to expressing strength per total volume. In certain cases, the primary and prominent expression of the total drug content per container would not be effective in preventing medication errors (e.g., insulin). Another example is the use of lidocaine or similar drugs for local anesthesia where the product is ordered and administered by percentage (e.g., 1% or 2%). In such cases, the total strength should be expressed: for example, 1% (100 mg/10 mL). Dry solids that must be reconstituted should follow the same format with the exception that only the total strength of the drug should be listed, not the strength/total volume or strength/mL.

### **Use of Leading and Terminal Zeros**

To help minimize the possibility of errors in drug dispensing and administration, when the quantity of active ingredient is expressed in whole numbers it shall be shown without a decimal point followed by a terminal zero (e.g., express as 4 mg, not 4.0 mg). When the quantity of active ingredient is expressed as a decimal number smaller than 1, it shall be shown with a zero preceding the decimal point (e.g., express as 0.2 mg, not .2 mg).

### **Labeling for Product Categories**

#### **Alcohol**

The alcohol content in a liquid preparation shall be stated on the label as a percentage (v/v) of C<sub>2</sub>H<sub>5</sub>OH.

### **Botanical Products**

The label of a herb or other botanical intended for use as a dietary supplement shall bear the statement, “If you are pregnant or nursing a baby, seek the advice of a health professional before using this product”.

### **Compounded Preparations**

The label on the container or package of an official compounded preparation shall bear a beyond-use date after which the compounded preparation should not be used. Because compounded preparations are intended for administration immediately or following short-term storage, their beyond-use dates may be assigned, in lieu of an expiration date, based on criteria that are different from those applied to manufactured drug products.

The monograph for an official compounded preparation typically includes a specified beyond-use date. The beyond-use date states the time following the date of compounding during which the preparation, when properly stored, can be used. In the absence of stability information, beyond-use dating should be assigned as recommended in Chapter *Pharmaceutical Compounding—Nonsterile Preparations* ( 795 ). (See *Stability Criteria and Beyond-use Dating* in general chapter *Pharmaceutical Compounding—Nonsterile Preparations* ( 795 ), *Stability of Compounded Preparations*).

### **Electrolytes**

The concentration and dosage of electrolytes for replacement therapy (e.g., sodium chloride or potassium chloride) shall be stated on the label in milliequivalents (mEq). The label of the product shall indicate also the quantity of ingredient(s) in terms of weight or percentage concentration.

### **Ferrules and Cap Overseals**

Healthcare practitioners using injectable products must be able to easily see and act on labeling statements that convey important safety messages critical for the prevention of imminent life-threatening situations. These cautionary labeling statements must be simple, concise, and devoid of nonessential information. Products that do not require cautionary statements should be free of information, so that those with cautionary statements are immediately apparent. Accomplishing this requires a systematic approach to labeling of injectable products, and one that assures that the ferrule and cap overseal—an area of these products that is highly visible to practitioners as they use these medicines—is reserved for

critical safety messages. Accordingly:

1. Only cautionary statements may appear on the top (circle) surface of the ferrule and/or cap overseal of a vial containing an injectable product. The cautionary statement should appear on both the ferrule and cap but may appear solely on the ferrule if the cap overseal is transparent and the cautionary statement beneath the cap is readily legible. A cautionary statement is one intended to prevent an imminent life-threatening situation and may include instructional statements that provide potency or other safety-related instructions if warranted. Examples of such statements include but are not limited to: “Warning—Paralyzing Agent” and “Dilute before Using.” The cautionary statement should be printed in a contrasting color and clearly visible under ordinary conditions of use.
2. If no cautionary statement is necessary, the top surface of the vial, including the ferrule and cap overseal, must remain blank.
3. Other statements or features including but not limited to identifying numbers or letters, such as code numbers, lot numbers, company names, logos, or product names, etc., may appear on the side (skirt) surface of the ferrule on vials containing injectable products but not on the top (circle) surface of the ferrule or cap overseal. The appearance of such statements or features on the skirt surface of the ferrule should not detract from, or interfere with, the cautionary statement on the top surface.

Official December 1, 2013

### **Neuromuscular Blocking and Paralyzing Agents**

All injectable preparations of neuromuscular blocking agents and paralyzing agents must be packaged in vials with a cautionary statement printed on the ferrules or cap overseals. Both the container cap ferrule and the cap overseal must bear in black or white print (whichever provides the greatest color contrast with the ferrule or cap color) the words: “Warning: Paralyzing Agent” or “Paralyzing Agent” (depending on the size of the closure system). Alternatively, the overseal may be transparent and without words, allowing for visualization of the warning labeling on the closure ferrule.

### **Parenteral and Topical Preparations**

The label of a preparation intended for parenteral or topical use shall state the names of all added substances (see *General Notices 5.20., Added Substances, Excipients, and*

*Ingredients*) and, in the case of parenteral preparations, also their amounts or proportions, except that for substances added for adjustment of pH or to achieve isotonicity, the label may indicate only their presence and the reason for their addition.

### **Aluminum in Large-volume Parenterals, Small-volume Parenterals, and Pharmacy Bulk Packages Used in Total Parenteral Nutrition Therapy**

1. The aluminum content of large-volume parenterals (LVPs) used in total parenteral nutrition (TPN) therapy must not exceed 25 µg/L.
2. The package insert of LVPs used in TPN therapy must state that the drug product contains no more than 25 µg of aluminum per L. This information must be contained in the *Precautions* section of the labeling of all LVPs used in TPN therapy.
3. If the maximum amount of aluminum in small-volume parenterals (SVPs) and pharmacy bulk packages (PBPs) is 25 µg/L or less, instead of stating the exact amount of aluminum that each contains, as in paragraph (4), the immediate container label for SVPs and PBPs used in the preparation of TPN parenterals (with exceptions as noted below) may state: "Contains no more than 25 µg/L of aluminum." If the SVP or PBP is a lyophilized powder, the immediate container label may state the following: "When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than 25 µg/L."
4. The maximum level of aluminum at expiry must be stated on the immediate container label of all SVPs and PBPs used in the preparation of TPN parenteral and injectable emulsions. The aluminum content must be stated as follows: "Contains no more than \_\_\_ µg/L of aluminum." The immediate container label of all SVPs and PBPs that are lyophilized powder used in the preparation of TPN solutions must contain the following statement: "When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than \_\_\_ µg/L." This maximum amount of aluminum must be stated as the highest one of the following three levels:
  - The highest level for the batches produced during the past three years
  - The highest level for the latest five batches
  - The maximum level in terms of historical levels, but only until completion of production of the first five batches after 26 July 2004.

The package insert for all LVPs, SVPs, and PBPs used in the preparation of TPN products shall contain the following statement in the *Warning* section of the label:

**WARNING:** This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature

neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions that contain aluminum. Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 µg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration of TPN products.

### **Potassium Chloride for Injection Concentrate**

The use of a black closure system on a vial (e.g., a black flip-off button and a black ferrule to hold the elastomeric closure) or the use of a black band or series of bands above the constriction on an ampoule is prohibited, except for *Potassium Chloride for Injection Concentrate*.

### **Salts of Drugs**

It is an established principle that official articles shall have only one official title (see separate compendial nomenclature requirements). For purposes of saving space on labels and because chemical symbols for the most common inorganic salts of drugs are well known to practitioners, the following alternatives are permitted in labeling official articles that are salts: HCl for hydrochloride; HBr for hydrobromide; Na for sodium; and K for potassium. The symbols Na and K are intended for use in abbreviating names of the salts of organic acids, but these symbols are not used when the word Sodium or Potassium appears at the beginning of an official title (e.g., Phenobarbital Na is acceptable, but Na Salicylate is not).

### **Special Capsules and Tablets**

The label of any form of Capsule or Tablet intended for administration other than by swallowing intact shall bear a prominent indication of the manner in which it should be used.

### **Products that Contain Vitamins**

The vitamin content of an official drug product shall be stated on the label in metric units per dosage unit. The amounts of vitamins A, D, and E also may be stated in USP Units. Quantities of vitamin A declared in metric units refer to the equivalent amounts of retinol (vitamin A alcohol). The label of a nutritional supplement shall bear an identifying lot number, control number, or batch number.

**Auxiliary Information** - Please [check for your question in the FAQs](#) before [contacting USP](#).