Guidance for Industry

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

DRAFT GUIDANCE

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For questions regarding this draft document contact (CDER), Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis, Carol Holquist at 301-796-0171.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2013
Drug Safety

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U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research

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Contains Nonbinding Recommendations

Draft – Not for Implementation

Guidance for Industry[1]

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to help prescription drug and biologic product manufacturers minimize medication errors[2] associated with their products. This guidance focuses on safety aspects of the container **label**[3] and carton **labeling** design, and provides a set of principles and recommendations for ensuring that critical elements of a product's container labels and carton labeling are designed to promote safe dispensing, administration, and use of the product.

This guidance applies to prescription drug and CDER-regulated biological products, including the following:

- Prescription drug products marketed under an approved new drug application (NDA) or abbreviated new drug application (ANDA);
- Prescription drugs marketed without an approved NDA or ANDA; and
- Biological products marketed under an approved biologics licensing application (BLA).

In this guidance, all such products are jointly referred to as *products*, and persons responsible for designing product container labels and carton labeling are referred to as *sponsors*. References to ***end user(s)*** include, but are not limited to, the patient, patient's caregiver, the prescribing physician, nurse, pharmacist, pharmacy technician, and other individuals who are involved in routine procurement, stocking, storage, and administration of medications (e.g., medication technicians).

[1] This guidance was prepared by the Division of Medication Error Prevention and Analysis in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer (National Coordinating Council for Medication Error Reporting and Prevention, http://www.nccmerp.org/aboutMedErrors.html).

[3] Terms that appear in bold type upon first use are defined in the Glossary section of this guidance.

This guidance does not apply to over-the-counter (OTC) drug products.

This is the second in a series of three guidance documents that the Food and Drug Administration (FDA) is issuing to help minimize medication errors. The first guidance focuses on minimizing risks associated with the design of the drug product and its **container closure system**.[4] The third planned guidance will focus on best practices for the development and testing of proposed **proprietary names** to minimize risks associated with drug product nomenclature, such as proprietary names that look or sound like the name of another product (e.g., look-alike or sound-alike names).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

Medication errors are a significant public health concern that account for an estimated 7,000 deaths annually in the United States.[5] In July 2006, the Institute of Medicine (IOM) published a report titled *Preventing Medication Errors.* The report cited labeling and **packaging** issues as the cause of 33 percent of all medication errors and 30 percent of fatalities from medication errors.[6] The IOM emphasized that "[p]roduct naming, labeling, and packaging should be designed for the end user — the provider in the clinical environment and/or the consumer."[7] More specifically, the report urged FDA to address safety issues related to product labeling and nomenclature using the principles of cognitive and human factors engineering.[8]

On September 27, 2007, the reauthorization and expansion of the Prescription Drug User Fee Act (PDUFA IV) was signed into law as part of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85). As part of the PDUFA IV reauthorization, FDA committed to certain performance goals, including measures to reduce medication errors related to look-alike and sound-alike proprietary names, unclear label abbreviations, acronyms, dose

[4] See the FDA draft guidance for industry *Safety Considerations for Product Design to Minimize Medication Errors* (December 2012). When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[5] Phillips DP, Christenfeld N, and Glynn LM. Increase in US Medication-Error Deaths between 1983 and 1993. The Lancet. 351:643-644, 1998.

[6] Aspden P, Wolcott JA, Bootman JL, Cronenwett LR, eds. *Preventing Medication Errors*. Institute of Medicine, The National Academies Press: Washington DC. 2006. Chapter 6: p. 275.

[7] IOM, *Preventing Medication Errors*. Chapter 6, Recommendation 4, p. 280.

[8] IOM, *Preventing Medication Errors.* Chapter 6, Actions to Improve Drug Naming, Labeling, and Packaging, p. 281-282.

designations, and error-prone labeling and packaging designs.[9] In June 2010, FDA held a public workshop and opened a public docket to receive comments on these topics.[10] This guidance and the companion guidances described in section I of this guidance present FDA's recommendations and conclusions after reviewing this public input.

III. GENERAL CONSIDERATIONS

The format and content of prescription drug and biological product labels and labeling must comply with FDA regulations in 21 CFR part 201 for drugs and 21 CFR part 610 Subpart G-Labeling Standards for biologics, and should conform with all labeling requirements required by the United States Pharmacopeia (USP). Although this guidance refers to some aspects of those requirements as they relate to the prevention of medication errors, product sponsors should refer to the regulations and USP for the full requirements.

A. Poor Design of Product Container Labels and Carton Labeling Can Obscure Critical Safety Information

Product container labels and carton labeling should communicate information that is critical to the safe use of a medication from the initial prescription, to procurement, preparation and dispensing of the product to the time it is given to the patient. Poor label design can contribute to medication errors by making it difficult for healthcare professionals, caregivers, and/or patients to readily locate and understand critical safety information. Examples from reports of medication errors include:

- Key information, such as the product name, strength, and dosage form, is missing; is expressed in a confusing manner; or is not prominently located and displayed.
- Key information does not appear in the same field of vision (i.e., the information is not readable without having to turn or rotate the container).
- Container labels and carton labeling look similar across multiple strengths of the same product or across multiple products within a company's product line.
- Container labels and carton labeling look similar among multiple products from different manufacturers.
- Container labels and carton labeling are visually cluttered by extraneous text or distracting images and graphics.
- Error-prone abbreviations or symbols are used.

[9] See letters from the Secretary of Health and Human Services to the Chairman of the Committee on Health, Education, Labor, and Pensions of the Senate and the Chairman of the Committee on Energy and Commerce of the House of Representatives, as set forth in the Congressional Record http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119243.htm.

[10] See April 12, 2010, Workshop Notice and Request for Comments (75 FR 18514), Docket No. FDA-2010-N-0168.

- Text is difficult to read because of font size or style, insufficient color contrast, or other design elements.

- Overlapping text is printed on both sides of a clear, transparent, or translucent container label such as those that might be found on syringes, ampules, vials, intravenous bags or low-density polyethylene (LDPE) vials.

B. Risk Assessment During the Design Stage Can Reduce the Risk of Medication Errors

It is important to consider the end users and their environment of use during the development and design of a drug product's label, labeling, and packaging. Sponsors should assess and minimize the risk of medication errors resulting from the design of product container labels and carton labeling before submitting proposed labels and labeling for FDA review and approval. Medication error risk assessment should take into account all of the prospective end users and the environments in which the product will be prescribed, dispensed, and used. FDA recommends applying the principles described in this guidance and testing the overall design using well-established risk assessment methods at the pre-IND stage or during the early stages of label, labeling, and packaging development, and when changes or additions to an already marketed drug product occur throughout the product's life cycle. For more information and recommendations on analytical methods for risk assessments, we refer you to the FDA draft guidance for industry *Safety Considerations for Product Design to Minimize Medication Errors* (see footnote 4).

C. Critical Product Information Should Appear on the Principal Display Panel

The **principal display panel** (PDP) is the panel of a label that is most likely to be displayed, presented, shown, or examined by the end user. We recommend that the PDP include the following critical information:

- Proprietary name
- **Established name** or **proper name**
- Product strength
- Route(s) of administration
- Warnings (if any) or cautionary statements (if any)

The information listed above should be the most prominent information on the PDP. Other information on the PDP such as the Rx-only statement, net quantity statement, manufacturer name, and logo should not compete in size and prominence with the important information listed above. Information such as the product strength equivalency statement, "each tablet contains" statement, and manufacturer name and logo is best placed on the side or back panel to maximize the prominence of the important information listed above.

D. Labels Should be Legible, Readable, and Easy to Understand

FDA recommends that the text on the container label and carton labeling should be (1) generally oriented in the same direction; (2) placed in the same field of vision (i.e., readable without having to turn or rotate the container); and (3) surrounded by adequate white space to improve **readability** and avoid crowding. For FDA regulations related to the readability of product labels, see 21 CFR 201.15. Important factors to consider include the following:

1. Container Label Size

The size of the container label greatly influences the overall container label design. FDA recognizes that in certain circumstances the container closure system might actually be inseparable from the container label (e.g., LDPE vial, glass ampule, syringe, blister foil backing, and intravenous bag). In other cases, the container label might be a paper, foil, or clear label that is affixed to the container closure system or blister. If the container label is too small, important information may not always fit on the principal display panel of the container label.

Ideally, manufacturers should explore approaches to create larger container labels or unique packaging to accommodate all critical information on the immediate product container label. FDA regulations provide an exemption from some drug labeling requirements when the container is too small or otherwise unable to accommodate a label with enough space to include all required information, provided that all required information is present on the carton labeling or in the prescribing information (21 CFR 201.10(i)). In such cases, the container label must include at minimum the product's proprietary and established name (if any); product strength; lot number; and the name of the manufacturer, packer, or distributor. USP requires the label of an **official drug product** to bear an expiration date.[11] Therefore, we also strongly recommend including the product's expiration date. For biological products, at a minimum, the name of the product, lot number, manufacturer name, and the recommended individual dose for multiple-dose containers must be included (21 CFR 610.60(c)). Such exemptions are not available, however, if the lack of space is caused by failure to use all available space on the container, or the use of label space is for non-required information or other design-related elements (see 21 CFR 201.15(a)(3) through (a)(5) and 201.15(b)).

2. Text Size and Style

Sponsors should choose a font that is easy to read, not lightweight or condensed. A number of published references recommend a larger font size such as 12-point sans serif (e.g., Arial) to improve readability.[12,13] FDA recommends the use of at least a 12-point font whenever label size permits.

[11] USP General Notices: 10. Preservation, Packaging, Storage, And Labeling;10.40.100; Expiration Date and Beyond-Use Date. USP has announced plans to relocate this information to General Chapter <7> *Labeling* in the near future.

[12] *Design for patient safety: A guide to the graphic design of medication packaging*, National Patient Safety Agency, Second Edition, 2007; *Design for patient safety: A guide to labeling and packaging of injectable medicines*, National Patient Safety Agency, Edition 1, 2008.

[13] Recommendations to the Safe Medication Use Expert Committee by the Health Literacy and Prescription Container Labeling Advisory Panel, May and November 2009, United States Pharmacopia (USP), posted April 2010.

3. Contrast of Text and Background Color

The color contrast between the text and the container label background color should be chosen to afford adequate **legibility** of the text. Sponsors should avoid color combinations that do not afford maximum legibility of text (e.g., pale yellow text on white container label background).

Text that is raised or recessed (i.e., embossed or debossed) on clear, transparent, or translucent containers (e.g., LDPE vials) is generally illegible. For these types of container labels, we recommend individually overwrapping the product so that a legible label is applied to the overwrap, and the product should be retained in the overwrap until it is administered.

4. Information Crowding and Visual Clutter

When labels are crowded, text size and prominence are generally decreased, and important information may be difficult to read and/or easily overlooked. Lines or blocks of text should be separated by sufficient white space to avoid crowding or clutter. We recommend placing less important information on a side or back panel of the container label and carton labeling, rather than on the PDP, or placing it, as appropriate, in the prescribing information.

Apart from required information about a product's manufacturer, distributor or packer (see § 201.1), information about business partnerships should not appear on the label or labeling.

The use of logos, bars, stripes, watermark graphics, lines, and symbols is discouraged on container labels and/or carton labeling because they can distract the reader from important information and add to label clutter. When such items are included, the graphic design should not compete with, interrupt, or distort important information.

We recommend not superimposing text over images or logos or placing a logo immediately before or after the proprietary name, because the logo can often look like an additional letter in the proprietary name. In addition, there should be no intervening written, printed, or graphic matter between the proprietary name, established name, and product strength (see § 201.10(a)).

Images of tablets and/or capsules can help pharmacists or other healthcare providers confirm they are dispensing the correct medication when comparing the product to be dispensed against the product contained in the commercial container closure system. If an image is used on the PDP, the image should appear at the bottom of the label and should not compete in size or prominence with the proprietary and/or **nonproprietary name** and strength information. Images should represent the actual tablet or capsule and reflect the true size, color, and imprint. Schematic or computer-generated images should not be used.

5. Dangerous Abbreviations, Acronyms, and Symbols

Certain abbreviations, acronyms, and symbols are dangerous and should not be used because they are frequently misinterpreted and can lead to mistakes that result in patient harm. For example, the abbreviation *µg* for microgram should not be used because it has been mistaken as *mg*, meaning milligram. The abbreviation *mcg* is an appropriate abbreviation for microgram. The abbreviation *IU* for international unit also should not be used because it has been confused for the intravenous route of administration. Mistakes can also result from the use of abbreviations, symbols, and dose designations whose meaning is non-standardized and/or unfamiliar to the healthcare professional or other target reader.[14] For these reasons, sponsors should avoid using error-prone abbreviations or symbols for product names, doses, and strength designations on container labels and carton labeling. We refer you to The Joint Commission's "Do Not Use" list, as well as the Institute for Safe Medication Practices (ISMP) List of Error-Prone Abbreviations, Symbols, and Dose Designations for a list of commonly confused abbreviations, symbols, and dose designations.[15,16,17]

E. Avoid Look-alike Container Labels and Carton Labeling

Look-alike container labels and carton labeling have frequently contributed to product selection errors leading to the dispensing and administration of the wrong drug, wrong strength and/or wrong dose. Sponsors should create a container label and carton labeling design that is sufficiently distinct from that of their other products and the products of other manufacturers so that the end user is able to correctly identify, select, dispense, and administer the appropriate medication, strength, and dose.

The potential for product confusion is especially problematic when products with similar looking container labels or carton labeling are customarily stored side-by-side or near one another. To reduce the risk of error, FDA recommends the following:

1. Corporate Trade Dress

Sponsors should avoid or minimize the use of **corporate trade dress** that could make it difficult for end users to distinguish between different medications or different strengths of the same medication.

[14] FDA/Institute for Safe Medication Practices Campaign to Eliminate Use of Error-Prone Abbreviations, http://www.ismp.org/tools/abbreviations/.
[15] The Joint Commission 2001; http://www.jointcommission.org/assets/1/18/Official_Do_Not_Use_List_6_111.PDF.
[16] The Institute for Safe Medication Practices' List of Error-Prone Abbreviations, Symbols, and Dose Designations, 2010, http://www.ismp.org/tools/errorproneabbreviations.pdf.
[17] USP General Chapters: <1265> Written Prescription Drug Information-Guidelines.

2. Use of Color

A common feature of look-alike products is the use of the same or similar colors in the container labels and carton labeling of multiple products across a company's entire product line or within a line of related products. We recommend that sponsors use color prudently to bring attention to the product name, strength, and important warning(s). Sponsors also should bear in mind that (1) individuals can perceive colors differently and some individuals may be colorblind, (2) identification of products by color might replace reading the label, (3) there are a limited number of discernible colors available, and (4) colors can look different under certain lighting conditions. Accordingly, color should not be the only element used as a means to distinguish different container label and carton labeling of multiple products across a company's entire product line or within a line of related products.[18]

In response to medication errors associated with the use of color on pharmaceutical product container labels, carton labeling, and packaging, FDA held a public hearing on March 7, 2005, to discuss the pros and cons of each of the following applications of color.[19] Based on these discussions, FDA recommends the following:

a. Color Differentiation

Color differentiation is an effective tool that can (1) differentiate products within a manufacturer's product line; (2) differentiate strengths within a manufacturer's product line; and (3) highlight certain aspects of the label, such as important warning statements. When applying color, sponsors should ensure that the text highlighted by the color has adequate color contrast against the background color. Color differentiation is most effective when the color used has no association with a particular feature and there is no pattern in the application of the color scheme.

b. Color Coding

Color coding is a technique that uses color to designate a specific meaning. FDA generally recommends avoiding color coding in most instances. 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.

The use of color coding on drug labels has been limited and not without risk. Color coding schemes developed to decrease error may actually increase error when the color is relied upon as a shortcut to proper identification (i.e., not reading the label). Errors can also occur when the color code is not meaningful to end users outside the limited environment where the color coding has an established use (e.g., Broselow Tape in the emergency room, and user-applied, color-coded labels in the operating room).

[18] Medication Errors, Second Edition, 2007, p. 119.

[19] See the *Federal Register* notice "Use of Color on Pharmaceutical Product Labels, Labeling, and Packaging; Public hearing," February 3, 2005 (70 FR 5687).

Certain applications of color coding are appropriate. Examples include the color coding of certain drug product strengths such as warfarin, levothyroxine, and conjugated estrogen-containing products. The colors of the strengths are universally color coded across all manufacturers. Another example is color coding the caps used for ophthalmic products to distinguish a therapeutic class (e.g., beta-blockers have a yellow cap). Although color coding the caps is useful to ophthalmologists and some patients in identifying the therapeutic class of medication, it is generally not helpful to end users outside of ophthalmology. In fact, the color coding has made it difficult for these users to differentiate between drugs *within* the same therapeutic class when the color code was used on the container label and carton labeling. Because these products are typically stored near each other, the similar appearance of the container labels and carton labeling has led to dispensing and administering the wrong strength, wrong dose, and wrong product. For these reasons, the color coding of ophthalmic products is limited to the cap color.

IV. SPECIAL CONSIDERATIONS AND RECOMMENDATIONS

A. Proprietary, Established, and Proper Names

Sponsors should maximize the readability of proprietary, established, and proper names on the container label and carton labeling. We recommend capitalizing only the first letter in the proprietary name because words written in all-capital letters are less legible than words written in mixed case letters. Moreover, the established or proper name and proprietary name should be displayed in a manner consistent with the FDA regulations, taking into account all pertinent factors, including typography, layout, contrast, and other printing features (for drugs see 21 CFR 201.10(g)(2)); for biologic products see 21 CFR 610.62).

The established name for drug products should include the finished dosage form. If space does not permit the finished dosage form to appear on the same line as the active ingredient, we recommend placing the finished dosage form on the next line below the active ingredient.

Mydrug (drugozide injection)	or	Mydrug (drugozide) injection	or	Mydrug (drugozide) Injection

For biological products, the proper name for biological products should not include the finished dosage form. The finished dosage form can appear on the line below the proper name.

Mydrug (drugozide) Injection	drugozide Mydrug Injection

Mixed case or **tall man lettering** on approved container labels and carton labeling can sometimes be used to help distinguish similar looking, established name pairs that have been confused postmarket. Dissimilar letters in each of the established names are placed in upper case

letters to bring attention to the point of dissimilarity between the names of concern (e.g., drugMY versus drug). We recommend that applicants consult FDA's medication error prevention staff before using this technique and supply data concerning the postmarket confusion concern, a description of how the letter string was selected, and data demonstrating that the proposed presentation will adequately distinguish between the potentially confusing product names. A list of approved name pairs that use mixed-case typography can be found on the FDA Web page at www.fda.gov/Drugs/DrugSafety/MedicationErrors/ucm164587.htm.

B. Product Strength

A product's strength or concentration is critically important information for the end user. If the product strength is not clearly displayed on the container label, or is expressed in units of measure that are incongruent with those used in the dosing instructions, the wrong strength can be selected or the wrong dose administered (i.e., over- or under-dosing). We recommend the following measures to avoid or minimize commonly reported dosing errors:

1. Strength Differentiation

Product selection errors leading to under- or over-dosing can occur when different strengths of the same product or similar strengths of different products are stored or displayed in close proximity. Sponsors should ensure that the product strength stands out on the container label and carton labeling. Appropriate techniques for this purpose include the use of boxing, a prominent typeface or type weight, and color differentiation, among others.

2. Strength Designation

Product strength designations should use a consistent unit of measure across all elements of the labeling (e.g., container, carton, and prescribing information). The product strength should match the units of measure described in the DOSAGE AND ADMINISTRATION section of the prescribing information to avoid error. For example, user confusion and dosing errors can occur if product strength is expressed on the label in percentage, but the directions for dosage and administration of the drug are expressed in milligrams. Sponsors also should use the same units of measure when labeling multiple products containing the same active ingredient (e.g., use *mg* for milligram to express the strength for all nitroglycerin products rather than using both mg and mcg).

3. Small Volume Parenteral Products

For small volume parenteral products, the product strength should be expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP, General Chapter <1> *Injection*.[20] A number of overdoses have occurred with small-volume

[20] USP General Chapter: <1> Injections; Labels and Labeling; strength and total volume for single- and multiple-dose injectable drug products. USP has announced plans to relocate this information to General Chapter <7> *Labeling* in the near future.

parenterals because of healthcare practitioner and patient failure to determine the total amount of drug in the container. In most cases, the user noticed the concentration (e.g., 10 mg/mL) but failed to see the net quantity (e.g., 10 mL), which often appears in a different location on the container label. This confusion has led to administration of the entire contents of the container, when only a portion of the total volume was needed.

To avoid such confusion, 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 milliliter enclosed by parentheses. For example:

500 mg/10 mL
(50 mg/mL)

If the product contains a volume of less than 1 mL, the product should never be labeled with a concentration of mg/mL, since this may lead end users to mistakenly think the container has more drug in it than it actually does, which can lead to under-dosing. For containers holding a volume of less than 1 mL, the strength per fraction of a milliliter should be the only expression of strength. For example:

12.5 mg/0.625 mL
or
12.5 mg per 0.625 mL

4. Expression of Strength for Dry Powder Products

Dry powder products should express the strength in terms of the total amount of drug per vial as follows:

XX mg/vial or XX mg per vial

Instructions for reconstituting the product and the resultant concentration should be included on the vial, if space permits. These instructions will inform persons responsible for preparing the product what type and volume of diluent should be used for reconstitution, and the amount of drug contained in each milliliter once reconstituted. If space permits, information on the expiration date and post-reconstitution storage should also be included.

5. Salt Nomenclature

When a product contains an active ingredient that is a salt, the USP Salt Policy should be applied when naming and labeling drug products.[21]

6. Prodrugs

For **prodrugs**, the product strength should be expressed in terms of the established or proper name of the prodrug — for example, Valtrex (valacyclovir hydrochloride tablets) is a prodrug for acyclovir. After oral administration, valacyclovir hydrochloride is rapidly absorbed from the gastrointestinal tract and nearly completely converted to acyclovir. Therefore, the strength of this product is based on valacyclovir rather than acyclovir.

7. Metric Measurements

The dose or expression of strength should appear in metric units of measure such as mL, mg, and mcg, rather than apothecary or household measurements (e.g., tsp for teaspoon, TBSP for tablespoon, drams, and grains) or ratios (e.g., 1:1000).

Fatal errors have occurred when healthcare providers or patients miscalculated medication doses when converting from one unit of measure to another (for example, the usual dose is expressed in terms of a milligram unit of measure, but the product strength is expressed as a ratio, requiring conversion of the ratio to a milligram dose).

8. Location of Net Quantity Statements

Product selection or dosing errors can occur if the net quantity statement is mistaken for the product strength, leading to under- or over-dosing. This error generally occurs when the product strength overlaps with the product net quantity (e.g., 100 tablets versus 100 mg) or when the net quantity is presented more prominently on the label than is the product strength. The net quantity statement should appear on the PDP but should be separate from and less prominent than the statement of strength (e.g., not highlighted, boxed, or bolded).

9. Leading and Terminal Zeros, Decimals, and Commas

Numbers containing decimal points in the declaration of strength can lead to tenfold dosing errors when the decimal point goes unseen (e.g., 4.0 mg is seen as 40 mg, or .4 mg is read as 4 mg). To minimize such errors, the quantity of active ingredient in the statement of strength should be presented in whole numbers, and not with a decimal point that is followed by a terminal zero (e.g., 4 mg, not 4.0 mg). Conversely, decimal numbers smaller than one should always be preceded by a zero (e.g., 0.4 mg, not .4 mg). This serves to enhance the visibility of the decimal point.

[21] USP General Chapters <1121> Nomenclature; Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations.

Commas should be used for numbers 1,000 and above to improve the legibility of larger numerals.

C. Route(s) of Administration

The route of administration should be described without abbreviation. We recommend using positive statements such as "for intravenous use," "give by subcutaneous injection," or "topical use only." Negative statements such as "NOT for intrathecal use" should not be used because it is easy to overlook the word "not," even when it is emphasized by bolding, underlining, or other means. Using affirmative statements will help to ensure that end users understand the intended route of administration, even if they do not read every word.[22,23,24]

D. Warnings for Critical Information

When warning statements are added to the container label or carton labeling, they should be written affirmatively. Non-affirmative warning statements have been confused. For example, the warning "Not for intrathecal use" has been confused as "For intrathecal use." Affirmative statements such as "For Intravenous Use Only," "Fatal if given by any other route," or "Must Dilute Before Use" are more easily understood.

E. Expiration Dates

Currently, manufacturers use various ways to express the expiration date on a product label. Some express the expiration date with the month and day, while others use the month and year. Most use abbreviations to express these dates (e.g., MA12). The use of abbreviations for expiration dates has led to confusion, misinterpretation, and sometimes delays in treatment because the abbreviation was interpreted incorrectly. For example: "MA" could mean March or May, whereas the number 12 could represent the day, month, or year. Accordingly, FDA recommends the expiration date be expressed in a standard format, using three-letter text for the month, two-digit numerals for the day (if included), and four-digit numerals for the year, as shown below:

MMMYYYY (e.g., JAN2013)

or

MMMDDYYYY (e.g., JAN012013)

F. Bar Codes

[22] Eastman Kodak Company. Ergonomic Design for People at Work, Second Edition. Chengalur SN, et al., eds. Hoboken, NJ: John Wiley & Sons, 2004.
[23] Handbook of Warnings. Wogalter MS, ed. Mahwah, NJ: Lawrence Erlbaum Associates, 2006.
[24] Proctor RW, Vu KL. Handbook of Human Factors in Web Design. United Kingdom: Routledge, 2005.

A bar code should be placed on the immediate container label and carton labeling of most drug products. The barcode should be surrounded by enough white space to allow scanners to read the bar code properly (see 21 CFR 201.25(c)(2)). Print density should be consistent to allow for an accurate scan. The bar code should be placed in a conspicuous location (e.g., not on the bottom of a carton) where it will not be difficult to read because of distorted text. Additionally, the barcode should be placed in an area where it will not be damaged because it appears at the point of label separation (e.g., perforation).

G. National Drug Code Numbers

Each listed drug product[25,26] is assigned a unique 10-digit, 3-segment number known as the national drug code (NDC). The NDC number identifies the labeler, product, and commercial package size.[27,28] When selecting the product code for NDC numbers of drug products with multiple strengths, FDA recommends the following:

Avoid assigning product codes that are numerically similar or identical. The similarity of the product code numbers has led to selecting and dispensing of the wrong strength and wrong drug. The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, assignment of sequential numbers for the middle digits is not an effective differentiating feature (e.g., 6666, 6667, and 6668), nor is using the identical product code for injectable products containing the same concentration of drug but different total volumes. For example, injectable products might contain the same product concentration but contain a different total amount of drug in the container because of differences in the fill volume (e.g., 20 mg/2 mL (10 mg/mL), 40 mg/4 mL (10 mg/mL)). When the same product code number is used for all of the different containers, healthcare practitioners have had difficulty distinguishing the difference in total drug content. Each of these injectable products should therefore have a different product code assigned. Another example is when injectable products contain the same concentration and same total drug content but delivers different volumes or doses. For example, a drug might be marketed in two prefilled pen devices, each containing a 10 mg/mL solution, and total volume of 3 mL. However, one device might deliver dosages of 5 mg (0.5 mL) and the other might deliver dosages of 10 mg (1 mL). Each of these prefilled pens should be assigned a different product code to help avoid confusion between the two products.

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[25] Under section 510 of the Federal Food, Drug and Cosmetic Act (FD&C Act) (21 U.S.C. 360), as amended, and part 207 of FDA's regulations, with some limited exceptions, firms that manufacture, prepare, propagate, compound, or process drugs in the United States or drugs that are offered for import into the United States must be registered with the FDA (see 21 U.S.C. 360(b), (c), (d), and (i)). Every person who registers must, at the time of initial registration, list all drugs manufactured, prepared, propagated, compounded, or processed for commercial distribution (21 U.S.C. 360(j)(1)) (see also 21 CFR 207.20). Drug listing information must be updated in June and December each year. These updates must include drugs not previously listed (if any), and certain changes to information for previously listed drugs (21 U.S.C. 360(j)(2); 21 CFR 207.21(b) and 207.30).

[26] Information regarding FDA's Drug Registration and Listing is available on FDA's Web site at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/DrugRegistrationandListing/default.htm.

[27] See 21 CFR 207.35(b)(3) for specific format requirements.

[28] Information regarding FDA's NDC Directory is available on FDA's Web site at http://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm.

If for some reason the middle digits cannot be revised, increase the prominence of the middle digits by increasing their size in comparison to the remaining digits in the NDC number or put them in bold type. For example: xxxx-XXXX-xx.

Avoid the reuse of NDC numbers. The reuse of NDC numbers has led to the dispensing and administration of the wrong drug or wrong strength.

H. Controlled Substance Schedule

Each commercial container of a controlled substance must prominently display the controlled substance schedule (i.e., CII through CV) as described in 21 CFR 1302.03 and 1302.04. The controlled substance schedule and the proprietary or established name should be separated by white space, not directly juxtaposed. For injectable drugs that are classified as Schedule IV controlled substances, FDA recommends the designation "CIV" rather than "C-IV." This is because "-IV" can be misread as an abbreviation for intravenous, leading to administration of the product by the wrong route, or as a number, leading to misinterpretation of the product strength as 4 mg.

V. OTHER SPECIAL CONTAINER LABEL AND CARTON LABELING CONSIDERATIONS

A. Unit Dose Blister Pack Presentations

Various configurations are available for products packaged in blister packs. For example, they can be a strip of individual blister cells (unit doses) or they can be a sheet containing multiple tablets for a particular duration of therapy (e.g., 3 days, 5 days, monthly). The size of a unit-dose blister is generally small, and blisters are often torn apart, punctured, or removed from the outer carton by the end user. Therefore, FDA recommends the following when developing the container label and carton labeling for these packs:

1. Blister Cell Label

Ideally, the proprietary and established name, strength, lot number, expiration date, bar code, and manufacturer should appear over ***each*** blister cell so that this important information remains available to the end user up to the point at which the last dose is removed. Each blister should include only one dosage unit per blister (e.g., one tablet, one capsule).

In certain cases it may not be possible to design the packaging to accommodate all critical information on each blister cell. In such circumstances, a random display of the information can appear multiple times across the back of the blister or the important information should be displayed in such a manner that it is not destroyed or eliminated when dosage units are removed.

2. Product Strength

The product strength on the principal display panel and other panels of the blister carton labeling should describe the milligram amount of drug per single unit (e.g., tablet, capsule) so that there is no confusion as to how much product is contained in a single unit as compared to the total contents of the entire blister card. We recommend the following:

XX mg per tablet or XX mg per capsule

3. Blister Cell Label Material and Readability

Color, type size, and font style should be carefully chosen based on the material used for the blister cell backing. Because the legibility of text printed on foil might be impaired due to the reflective nature of the material, it is important to ensure that information printed on foil is readily legible. When possible, a non-reflective material should be used to enhance readability of product information.

4. Blister Pack Label Design

Careful consideration should be given to the overall design of a blister pack label so that it does not lead to confusion and error. Sponsors should limit the number and variety of blister packs, and ensure that the packaging configuration makes sense for the dosage and administration of the drug product and the intended patient population. Although special packaging for specific treatment regimens might improve patient compliance and minimize the risk of accidental exposures to the drug, they can also be confusing and prone to dosing errors if not designed properly. Blister labeling design factors that have been associated with reported medication errors include, but are not limited to, the following:

- Presenting and sequencing doses in ways that do not match the product's approved usual dosage, leading to administration of the wrong dose. For example, the blister labeling presents the product or labels the product in a manner that provides for a fixed dose (e.g., twice-a-day dose) but the approved usual dosing regimen is variable (e.g., once or twice daily).

- Labeling doses in the package with days of the week when the dosage and administration does not require such sequencing. For example, a packaging configuration labeled with the days of the week (e.g., Mon., Tues., and Wed.) can lead to delays in starting therapy because patients wait to start their medication on the first specified day.

- Numbering each blister cell in sequence, such as controlled substances packaged in a 30-tablet blister pack and numbered from 1 to 30. Although this may be convenient for record keeping of controlled substances in facilities, the number has been confused for the tablet strength.

- Providing more doses than needed for a single course of treatment, leading to excessive duration of therapy (e.g., a 20-tablet pack for a product that should be administered once daily for a total of 5 days).

B. Labeling of Ferrules and Cap Overseals

Vials for injectable drug products often include elastomeric closures (stoppers), which are connected to the vials by bands, or *ferrules*. A cap overseal is a disc over a ferrule that protects the stopper. The ferrule and cap should be prominently visible on the vial immediately before administering the drug product. Given their location, the information provided on ferrules and caps of medication vials has a critical role in providing crucial information to the healthcare provider and should be limited to important safety messages critical for the prevention of imminent, life-threatening situations. If no cautionary statement is necessary, the top surface of the vial, including the ferrule and cap overseal, should remain blank. Other statements (e.g., lot numbers) can appear on the side of the ferrule but should not detract from any cautionary statement appearing on the top surface.

The USP created a Labeling on Ferrules and Cap Overseals section of General Chapter <1> *Injections*, which will become official on December 1, 2013. Applicants and sponsors should comply with the recommendations set forth in the revised USP General Chapter <1>.[29]

C. Color Closure System for Concentrated Potassium Chloride

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 ampule, is used only for Potassium Chloride for Injection Concentrate. This unique color closure system differentiates this concentrated strength of potassium chloride from other less concentrated strengths of potassium chloride and alerts the end user that the product is more concentrated.[30] As such, a black cap/ferrule/lines should not be used on any other drug product.

D. Labels for Large Volume Parenterals

FDA receives many reports of confusion and errors involving large-volume parenteral products. These reports cite similarity of the containers, lack of prominence of important information on the label, and label clutter. These concerns were addressed at a joint public meeting held by FDA, ISMP, and USP in 2007.[31] Based on the information and recommendations presented at the public meeting, FDA considers the following information to be essential for the container label of large volume parenterals:

- Name and strength
- Statement "Do not add supplementary …to the Y port…"
- Statement "Sterile"

[29] USP General Chapters; General Test and Assays <1> Injections; Packaging Containers for Injections. USP has announced plans to relocate this information to General Chapter <7> *Labeling* in the near future.

[30] USP General Chapters; General Test and Assays <1> Injections; Packaging Containers for Injections. USP has announced plans to relocate this information to General Chapter <7> *Labeling* in the near future.

[31] See the *Federal Register* notice "Improving Patient Safety by Enhancing the Container Labeling for Parenteral Infusion Drug Products; Public Meeting," November 28, 2006 (71 FR 68819).

- Statement "Each 100 mL contains….."
- General and/or Special Storage Requirements such as:
    - "See USP Controlled Room Temperature"
    - "Protect from Freezing" should only be used if the drug product is adversely affected by freezing[32]
- Labels of Ports (e.g., arrows with "med" or "set")
- Barcode
- Lot number and Expiration Date
- Recycling code symbol
- Statement "For use only with a calibrated infusion device"
- Revision date
- "See prescribing information" (not "see package insert")
- "Additive compatibility, consult pharmacist" (not "Compatibility of additives, check with a pharmacist")

The following information is considered label clutter and should not be included on the large volume parenteral container label or presented, as appropriate, in the prescribing information:

- All secondary trademark information (e.g., "VisIV", "Intravia" Container)
- Symbols (e.g., circles that represent strength) should not be included on the container label or in the prescribing information
- Statements such as "Caution – check for minute leaks by squeezing container firmly…" and "If leaks are found…"
- Statement "Use only if solution is clear and container is undamaged"
- Statements about "series connection" should not be included on the container label or in the prescribing information
- Osmolarity statement
- Lactic acidosis statement (e.g., on lactated ringers bags)
- Statements such as "printed in USA"
- Manufacturer full address
- Statements such as "Dose intravenously as directed by physician" should not be included on the container label or in the prescribing information
- Statement "Whenever possible use central route"
- pH statement
- Blood transfusion warning
- Statements such as "non-pyrogenic"
- Warnings for purposes of interstate commerce should not be included on the container label or in the prescribing information

[32] USP General Notices: *10.30.90. Protection From Freezing.* USP has announced plans to relocate this information to General Chapter <7> *Labeling* in the near future.

E. Transferable or Peel-Off Labels for Injectable Medications

Currently, once an injectable medication is withdrawn from the commercial container closure (e.g., vial or ampule) into a syringe for administration, the syringe no longer provides information needed by the end user to verify the drug name and strength prior to administration. Such unlabeled medication has led to administration of the wrong drug and wrong strength.

FDA recommends that sponsors develop, when possible, a transferable or peel-off label for the commercial container of injectable products. This type of label can help to minimize the use of unlabeled syringes because the label would be attached to the commercial container closure, present at the point of product preparation, and not be discarded as in the case with other auxiliary labels often provided with the carton.

F. Double-sided Labels and Labeling

Printing information on both the front and back panels of labels and labeling can be an effective way to present safety information and, if done correctly, can help prevent medication errors. When double-sided printing is used on clear, transparent, or translucent labels and labeling, such as LDPE vials or intravenous bags, the text should be readable in both the upright and inverted positions and should not overlap with other text.

G. Pharmacy Bulk Packages

For Pharmacy Bulk Packages (PBPs), a prominent, boxed declaration reading "Pharmacy Bulk Package – Not for Direct Infusion" should be placed on the principal display panel following the expression of strength. This statement can be made more prominent by using boldface type, large size type, or a contrasting color. The container label for PBPs should not include graduation marks.

H. Communication of Important Product Changes

Changes to marketed products such as new strengths or concentrations, or changes in formulation, or changes in certain inactive ingredients should be communicated to health practitioners on the container label, if space permits, and on the carton labeling. For example, a change in product strength should be communicated as "New Strength" or "Note New Strength." This statement should appear on the principal display panel for a period of 6 months.

I. Dosing Devices

Dosing devices included with a drug product should be appropriate for the dosages to be measured.[33] The dosing device should deliver an oral solution in a volumetric unit of measure,

[33] See the FDA guidance for industry *Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products* addresses issues concerning dosing devices for OTC liquid drug products (available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

preferably milliliters (mL), consistent with recommended dosing. For example, sponsors should not create an oral syringe that is calibrated in milligrams rather than milliliters.

J. Product Samples

Each product sample unit must bear a label that clearly denotes its status as a drug sample (e.g., "sample," "not for sale," "professional courtesy package" (21 CFR 203.38(c)). At a minimum, product sample labels must also include the proprietary and nonproprietary names; product strength; lot number; and the name of the manufacturer, packer, or distributor of the drug (21 CFR 201.10(i)). We also strongly encourage including the expiration date and NDC number. Professional samples packaged as packs or kits should not be labeled with terms such as *starter*, *starter samples*, and *patient starter pack*.[34] In addition, the sponsor should consider providing a blank open space on the label so the provider of the drug sample can write or affix a label with the patient name and specific instructions for use.

K. Package Type

Including the **package type** on container labels and carton labeling (e.g., single-dose and pharmacy bulk packages) is important in situations where it is unclear how the medication should be safely handled and used simply by viewing the container. For example, vials containing a specific quantity of a drug product intended to be used as a single dose on a single patient should include the term single dose on the vial to differentiate them from multiple-dose vials and alert the user to the appropriate use of the product.

In addition, when the product appears to be in a child-resistant container (e.g., unit-dose blister) but the container is NOT in fact child-resistant, it is important to include a statement on the label indicating the package is not child-resistant. For example, "This package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be used."

USP General Chapter <659> *Packaging and Storage Requirements* includes package-type terms and definitions.

L. Quick Response Code

A Quick Response Code (QR code) is a type of matrix bar code (or two-dimensional bar code) that can be read by a mobile phone. QR codes may provide various bits of information (e.g., Internet address, phone numbers). FDA has not developed a formal position on the use of QR Codes. If a manufacturer uses a QR code, we recommend that it appear on the side or back panel of the container label or carton labeling, away from the bar code and in a size that does not compete with, distract from the presentation of other required or recommended information on the label.

[34] See the final rule "Prescription Drug Marketing Act of 1987; Prescription Drug Amendments of 1992; Policies, Requirements, and Administrative Policies" (December 3, 1999, 64 FR 67720 at 67742), available at http://www.gpo.gov/fdsys/pkg/FR-1999-12-03/pdf/99-30954.pdf.

GLOSSARY

Container Closure System: A *container closure system* refers to the sum of packaging components that together contain and protect the dosage form. This includes 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.

Corporate Trade Dress: As used in this guidance *corporate trade dress* means the manner in which a company packages, wraps, and labels, a drug or biologic product including the use of color schemes, sizes, designs, shapes, and placements of words or graphics on a container label and/or carton labeling.

End user: *End users* include, but are not limited to, the patient, patient's caregiver, the prescribing physician, nurse, pharmacist, pharmacy technician, and other individuals who are involved in routine procurement, stocking, storage, and administration of medications (e.g., medication technicians).

Established Name: Section 502(e)(3) of the FD&C Act (21 U.S.C. 352) states that "the term 'established name,' with respect to a drug or ingredient thereof, means (A) the applicable official name designated pursuant to section 508 [(21U.S.C. 358)], or (B) if there is no such name and such drug, or such ingredient, is an article recognized in an **official compendium** [see definition below], then the official title thereof in such compendium, or (C) if neither clause (A) or clause (B) of this subparagraph applies, then the common or usual name, if any of such drug or such ingredient, except that where clause (B) of this subparagraph applies to an article recognized in the United States Pharmacopeia and in the Homeopathic Pharmacopeia under different official titles, the official title used in the United States Pharmacopeia shall apply unless it is labeled and offered for sale as a homeopathic drug, in which case the official title used in the Homeopathic Pharmacopeia shall apply."

Label: As defined in section 201(k) of the FD&C Act (21 U.S.C. 321(k), the term *label* means a display of written, printed, or graphic matter upon the immediate container of any article, or is easily legible through the outside container or wrapper.

Labeling: As defined in section 201(m) of the FD&C Act, the term *labeling* means "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."

Legibility: *Legibility* is concerned with how easy it is to distinguish individual letters. Legibility is dependent on the typeface design.

Official Drug Product: USP General Notices, Section 2.20, Official Articles defines an *official product* as a drug product, dietary supplement, compounded preparation, or finished device for which a monograph is provided.

Official Compendium: Defined in section 201(j) of the Act as "the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, official National Formulary, or any supplement to any of them."

Package Type: For the purposes of this guidance, the *package type* is a description of the container-closure system that drug substances and final drug dosage forms are contained in.

Packaging: A *package* or *market package* refers to the container closure system and labeling, associated components (e.g., dosing cups, droppers, spoons), and external packaging (e.g., cartons or shrink wrap). A market package is the article provided to a pharmacist or retail customer upon purchase and does not include packaging used solely for the purpose of shipping such articles.

Principal Display Panel: The term *principal display panel* refers to 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.

Prodrugs: *Prodrugs* are products that are converted to another active moiety once ingested.

Proper name: For biological products, the *proper name* means the name designated in the license for use upon each package of the product (21 CFR 600.3(k)).

Proprietary Name: The exclusive name of a drug substance or drug product owned by a company under trademark law regardless of registration status with the Patent and Trademark Office.

Readability: *Readability* refers to the ease with which a reader can scan over paragraphs of type. Readability is dependent on the manipulation or handling of the type. A highly legible typeface can be made unreadable by poor typographic design. Factors that affect readability include: line lengths, point size, leading, typeface selection, spacing, type alignment, and background.

Tall Man Lettering: *Tall man lettering* involves highlighting the dissimilar letters in two names to aid in distinguishing between the two.[35]

[35] Institute of Safe Medication Practices, http://www.ismp.org/faq.asp#Question_8.