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

Guidance for Industry

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

May 2022
Drug Safety

GRZAN

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Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to help human prescription drug and biological product sponsors, application holders, and applicants minimize medication errors[2] associated with their products. This guidance focuses on safety aspects of the application holder's[3] container **label**[4] and carton **labeling** design. It provides a set of principles and recommendations for ensuring that critical elements of a product's container label and carton labeling are designed to promote safe dispensing, administration, and use of the product.

This guidance applies to human prescription drug and biological products, including the following:[5]

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

[2] A medication error is any preventable event that may cause or lead to inappropriate medication use or medication-related patient harm while the medication is in the control of the health care professional, patient, or consumer (see also National Coordinating Council for Medication Error Reporting and Prevention, "About Medication Errors," n.d., https://www.nccmerp.org/about-medication-errors).

[3] In this guidance, we primarily use the term *sponsor* to describe the person or entity responsible for the content of the container label and carton labeling. For the purposes of this guidance, sponsor, application holder, and applicant include entities marketing unapproved, new prescription drugs, even though such drug products are not the subject of an approved application.

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

[5] Although this guidance focuses on container labels and carton labeling considerations for drug and biological products, the recommendations are also relevant to combination products regulated by CDER and CBER. For additional information regarding product-specific labeling requirements, sponsors should contact the CDER or CBER review division responsible for the application.

- Prescription drug products marketed under an approved new drug application or abbreviated new drug application[6]
- Prescription drugs marketed without an approved application
- Biological products marketed under an approved biologics license application

In this guidance, all such products are jointly referred to as *products, drugs,* or *drug products* unless otherwise specified, and persons responsible for designing product container labels and carton labeling are referred to as *sponsors*. References to ***end users*** include, but are not limited to, the patient; the patient's caregiver; and the physician, nurse, pharmacist, pharmacy technician, and other individuals who are involved in the routine procurement, stocking, storage, selection, dispensing, preparation, and/or administration of prescription medications (e.g., medication technicians).

Although this guidance does not apply to over-the-counter drug products, compounded products, marketed prescription products used in clinical or bioequivalence studies, or investigational products, the principles outlined in this guidance may still be useful for such products.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

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 medication errors and 30 percent of fatalities from medication errors that were reported to the Institute for Safe Medication Practices (ISMP).[7] 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."[8] More specifically, the report urged FDA to address safety issues related to

[6] Some recommendations may not apply to positron emission tomography drug products. See FDA guidances *FDA Oversight of PET Drug Products Questions and Answers* (December 2012) and *PET Drugs—Current Good Manufacturing Practice (CGMP)* (December 2009) for additional information. We update guidances periodically. For the most recent version of the guidances, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[7] Aspden, P., Wolcott, J. A., Bootman, J. L., and Cronenwett, L. R., eds., *Preventing Medication Errors*, IOM, Washington, DC: The National Academies Press, 2006, p. 275.

[8] *Id*. at p. 280.

product labeling and nomenclature using the principles of cognitive and human factors engineering.[9]

On September 27, 2007, the reauthorization and expansion of the Prescription Drug User Fee Act was signed into law as part of the Food and Drug Administration Amendments Act of 2007 (Public Law 110-85). As part of the Prescription Drug User Fee Act 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, and dose designations; and error-prone labeling and packaging designs.[10] In June 2010, FDA held a public workshop and opened a public docket to receive comments on these topics.[11] This guidance presents FDA's recommendations and conclusions after having reviewed this public input and considered information learned through postmarketing medication errors over the ensuing years.

III. GENERAL CONSIDERATIONS

The format and content of prescription drug and biological product labels and labeling must comply with the applicable provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 301 et seq.); FDA regulations in 21 CFR part 201, for drugs; and FDA regulations in 21 CFR part 610, Subpart G, Labeling Standards, for biological products. In addition, the format and content of prescription drug and biological product labels and labeling must conform to United States Pharmacopeia (USP) labeling requirements in certain cases. 21 U.S.C. § 352(g).[12] In such cases, sponsors are responsible for referring to the regulations and USP for applicable requirements. This guidance provides recommendations for products not covered by those requirements.

The development of labels and labeling is product-specific, and the risk for medication errors differs between products and can be impacted by many factors. Although this guidance provides a set of principles and recommendations for ensuring that critical elements of a product's container label and carton labeling are designed to promote safe dispensing, administration, and use of the product, the considerations described are intended to support flexibility where appropriate. To that end, FDA strongly encourages sponsors to discuss product-specific design

[9] *Id.* at p. 281–282.

[10] 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, at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119243.htm.

[11] See *Workshop Notice and Request for Comments*, published on April 12, 2010 (75 FR 18514).

[12] For drug products with an applicable USP/NF monograph, USP General Chapters numbered below 1000 are requirements if referenced in the drug's USP/NF monograph; otherwise, they are recommendations. (See USP General Notices 3.10 (2021)). Sponsors should familiarize themselves with whether the noted USP citations throughout this guidance apply as a requirement for their specific product(s).

questions with FDA via appropriate regulatory pathways as early as feasible in the product development timeline.[13]

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 and effective use of a medication throughout the medication use process (i.e., initial prescription, procurement, preparation, dispensing of the product, administration to the patient). Poor label or labeling design can contribute to medication errors by making it difficult for end users to readily locate and understand critical safety information. Examples from reports of medication errors related to poor design of container labels or carton labeling include:

- Key information, such as the product name(s)[14], **dosage form**(s), and strength(s), 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.
- Text is difficult to read because of font size or style, insufficient color contrast, or other design elements (e.g., embossing, debossing).
- 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, or intravenous bags.

[13] See FDA draft guidances for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (December 2017) and *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products Guidance for Industry* (June 2018). When final, these guidances will represent the FDA's current thinking on this topic. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[14] For the purposes of this guidance, *product name* can refer to a proprietary name, established name, or proper name (see the Glossary for definitions of these terms).

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

It is important to consider the intended uses, 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, as appropriate, evaluating the overall design using well-established risk assessment methods throughout the development of the label, labeling, and packaging to minimize the risk of medication errors. This can begin as early as the pre-Investigational New Drug stage and should occur when changes or additions to an already-marketed drug product occur throughout the product's life cycle. For more information and recommendations on packaging approaches and analytical methods for risk assessments, we refer you to the FDA guidance for industry *Safety Considerations for Product Design to Minimize Medication Errors* (April 2016).

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

For the purposes of this guidance, the **principal display panel** (PDP) is the panel of a container label or carton labeling that is most likely to be displayed to, presented to, shown to, or examined by the end user. The information on the PDP allows for proper identification of the product. We recommend that the PDP include the following critical information:

- Proprietary name, if there is one
- **Established name** or **proper name**
- Dosage form[15]
- Product strength
- Route(s) of administration
- Warnings (if any) or cautionary statements (if any)[16]
- Controlled substance schedule if the product is a controlled substance

The information listed above should be the most prominently displayed information on the PDP. For injectable products, the package type term should be included on the PDP, if space permits (see section V.K. below).[17] In some cases, frequency of dosing statements (e.g., *once daily* for extended-release oral products that are dosed once a day) may also be considered for inclusion on the PDP when there is concern that frequency errors may occur. If included, the frequency of dosing statement should not be in the same location as, or immediately following, the product

[15] Established names for drug products typically include the dosage form. We include dosage form in the list because proper names for biological products typically do not include a dosage form.
[16] See Section IV. E for examples of warnings and cautionary statements.
[17] For more information about package type terms, see the FDA guidance for industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018).

strength. This is to minimize the risk of misinterpreting the combination of strength and frequency of dosing as the complete dosing instruction (e.g., juxtaposing tablet strength (20 mg) with dosing frequency (once daily) would yield *20 mg once daily*, which would be misleading for a product that is supposed to be dosed 40 milligrams (mg) (2 tablets) once daily). Other information on the PDP, such as the *Rx only* statement, net quantity of contents statement (hereafter referred to as *net quantity*), manufacturer name, and manufacturer logo should not compete in size and prominence with the information listed above. Sponsors can use side or back panels for information such as the product strength equivalency statement, *each tablet contains* statement, lot number, expiration date,[18] and recommended dosage to maximize the prominence of the information listed above.

D. Container Labels and Carton Labeling Should be Legible, Readable, and Understandable

FDA recommends that the text on the container label and carton labeling 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 sufficient blank space to improve **readability** and to avoid crowding. For FDA regulations related to the readability of product labels, see § 201.15 (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., low-density polyethylene ampules, intravenous bags). 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 PDP of the container label.

FDA encourages sponsors to explore approaches for creating sufficiently large container labels or unique packaging to accommodate all critical and required information on the immediate product container label. FDA regulations provide an exemption from some drug product labeling requirements when the container is too small or otherwise unable to accommodate a label with enough space to include all required information so long as certain information is included and all required information is present on the carton labeling or in the Prescribing Information (PI) (§ 201.10(i)). For related provisions, see 21 CFR 201.10(h)(2), 21 CFR 610.60(c) and (d)).

In such cases where the container label is too small or unable to accommodate an adequately sized label, the container label for drug products must include, at minimum, the product's

[18] Drugs that meet the definition of *product* as defined under section 581(13) of the FD&C Act (21 U.S.C. 360eee(13)) require a product identifier (defined in section 581(14) of the FD&C Act) to be affixed or imprinted in human- and machine-readable format. The product identifier consists of the product NDC, serial number, lot number, and expiration date. See section 582(b)(2) and (e)(2) of the FD&C Act (21 U.S.C. 360eee-1(b)(2) and (e)(2)) for product identifier requirements.

proprietary name (if any) and established name; lot or control number; and the name of the manufacturer, packer, or distributor (see 21 CFR 201.10(i)). For related provisions, see 21 CFR 201.10(h)(2), 21 CFR 610.60(c) and (d)). Although FDA requirements for partial labels do not require the inclusion of an expiration date, we note that, regardless of size, USP requires the label of an **official drug product** to bear an expiration date.[19] Therefore, even for products to which the USP requirement does not apply, we also strongly recommend including the product's expiration date. The exemptions described in § 201.10(i) are not available 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 information that is not required or other design-related elements (see § 201.15(a)(3) through (a)(5) and § 201.15(b)). For biological products, at a minimum, the label must include the name of the product (expressed either as the proper or common name), lot number or other lot identification, manufacturer name, and the recommended individual dose for multiple-dose containers (§ 610.60(c) (21 CFR 610.60(c))).[20] For identification purposes and to minimize the risk for medication error, we also strongly recommend that the product strength be included for both drug and biological products.

When applicable, such as with an injectable product, sponsors must also ensure that when a label has been affixed to the container, a sufficient area of the container is uncovered for its full length or circumference to permit inspection of the contents (§ 610.60(e)).[21]

2. Text Size and Style

Where feasible for container labels and carton labeling, sponsors should choose fonts that are not lightweight (i.e., thin font) or condensed such that legibility is compromised. A number of published references recommend a larger font size, such as 12-point sans serif (e.g., Arial), to improve readability.[22, 23] FDA recommends the use of an appropriate size and style of font that improves readability within the confines of the label size.

3. Contrast of Text and Background Color

The color contrast between the text and the container label or carton labeling background color on top of which text may be placed should be chosen to afford adequate **legibility** of the text.

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[19] USP General Chapter <7>, Labeling. Vaccine labeling is not included in this general statement.

[20] Biological product regulations for full and partial labels of containers do not require the dosage form. However, FDA recommends that dosage forms be included on partial labels if space permits. For certain products (e.g., vaccines for infectious disease indications) we recommend inclusion of the route of administration rather than dosage form if space permits.

[21] For more information for injectable drug products, see USP General Chapter <7>, Labeling.

[22] National Patient Safety Agency, *Information Design for Patient Safety: A Guide to the Graphic Design of Medication Packaging,* 2nd edition, 2007; National Patient Safety Agency, *Design for Patient Safety: A Guide to the Labelling and Packaging of Injectable Medicines*, 1st edition, 2008.

[23] USP, *Recommendations to the Safe Medication Use Expert Committee by the Health Literacy and Prescription Container Labeling Advisory Panel*, May and November 2009.

Sponsors should avoid color combinations that do not afford adequate legibility of text (e.g., pale yellow text on white container label background). Additionally, sponsors should consider the substrate on which the text will be printed (e.g., matte versus gloss finish) because this can also impact the legibility of the text. Text that is raised or recessed (i.e., embossed or debossed), without color, on clear, transparent, or translucent containers (e.g., low-density polyethylene ampules) is generally illegible. For these types of container labels, we recommend individually overwrapping each unit so that a legible label is applied to the overwrap, and the product should be retained in the overwrap until it is administered. The overwrap should include all of the critical product information discussed in section III.C above as well as a linear barcode (see section IV.G below). Additionally, embossed or debossed text should not be used on pouch or overwrap labeling (e.g., debossing the lot number and expiration date).

4. Information Crowding and Visual Clutter

When container labels or carton labeling are crowded, text size and prominence are generally decreased, and important information may be difficult to read or easily overlooked. Lines or blocks of text should be separated by sufficient blank space to avoid crowding or clutter. We recommend placing noncritical 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 PI.

The use of logos, stripes, watermark graphics, lines, and symbols on container labels and/or carton labeling may help to differentiate products, but it should not distract the reader from critical information or add to label clutter. When such items are included, the graphic design should not compete with, interrupt, or distort critical 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 look like an additional letter in the proprietary name. In addition, there must not be intervening written, printed, or graphic matter between the proprietary name and established name (21 CFR 201.10(a)) and there should be no intervening written, printed or graphic matter between a proper name and its trade name (see 21 CFR 610.62 regarding information crowding and visual clutter) and product strength. Note that FDA does not consider trademark symbols associated with proprietary names (e.g., registered trademark symbols (®), unregistered trademark symbols (™) or controlled substance symbols (e.g., CII)) to be intervening matter.

Images of oral dosage forms (e.g., tablets, capsules) may help pharmacists or other health care providers confirm they are dispensing or restocking the correct medication when comparing the product to be dispensed or restocked against the product contained in the commercial container closure system. If an image is used on the PDP, we recommend that it appear at the bottom of the label and not compete with the product name(s) and strength information. The image should

be the same one submitted in the Structured Product Labeling file[24, 25] and reflect the actual size, shape, color, and code imprint[26] for the dosage form.

5. Error-Prone Abbreviations, Acronyms, and Symbols

Certain abbreviations, acronyms, and symbols should not be used on container labels or carton labeling because they are frequently misinterpreted and can lead to medication errors that result in patient harm.[27] For example, the abbreviation *μg* for microgram should not be used because it has been mistaken as *mg*, meaning *milligram*.[28] 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.[29] Errors can also result from the use of abbreviations, symbols, and dose designations whose meaning is nonstandardized or unfamiliar to the health care professional or other end user.[30] 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.[31, 32] We refer you to the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations for a list of frequently misinterpreted abbreviations, symbols, and dose designations.[33]

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

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[24] See FDA guidance for industry *Providing Regulatory Submissions in Electronic Format—Drug Establishment Registration and Drug Listing* (May 2009).

[25] For information on submitting images in the Structured Product Labeling file, visit the U.S. National Library of Medicine SPL Image Guidelines at https://dailymed.nlm.nih.gov/dailymed/splimage-guidelines.cfm.

[26] Under 21 CFR 206.10, a code imprint is required on most solid oral dosage forms marketed in the United States. A code imprint means any single letter or number or any combination of letters and numbers, including, e.g., words, company name, and NDC; a mark, symbol, logo, or monogram; or a combination of letters, numbers, and marks or symbols, assigned by a drug firm to a specific drug product. The code imprint, in conjunction with the product's size, shape, and color, permits the unique identification of the drug product and the manufacturer or distributor of the product.

[27] ISMP, "List of Error-Prone Abbreviations," October 2, 2017, https://www.ismp.org/recommendations/error-prone-abbreviations-list.

[28] *Id.*

[29] *Id.*

[30] FDA ISMP Campaign to Eliminate Use of Error-Prone Abbreviations (http://www.ismp.org/tools/abbreviations/).

[31] Historically, a slash (/) has been used in strength presentations (e.g., 50 mg/5 mL); thus, health care practitioners are familiar with the use of slashes in these circumstances. The use of slash marks for strength presentations is generally acceptable.

[32] For safety reasons, we also recommend avoiding the use of error-prone abbreviations, acronyms, and symbols in the PI and drug advertising or promotion.

[33] See also USP General Chapter <1265>, Written Prescription Drug Information—Guidelines.

sufficiently distinct from that of their other products 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

When a sponsor uses **corporate trade dress** to, for example, distinguish their product from another sponsor's product, the trade dress should be designed in a manner that ensures that information on the label is legible, readable, and not subject to confusion. Sponsors should consider whether the use of corporate trade dress could make it difficult for end users to distinguish between different medications or different strengths of the same medication within their product lines, and should ensure there are means to distinguish the container labels and carton labeling of multiple products (see also section III.E.2 below).

2. Use of Color

A commonly cited contributing factor in reported medication errors involving 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 product line or within a line of related products. We recommend that sponsors use color prudently to bring attention to the product name(s), strength, and important warnings or cautionary statements, as appropriate. Sponsors also should bear in mind that: (1) individuals can perceive colors differently, and some individuals may have color vision deficiency; (2) the 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.[34] Other means of distinguishing among container labels and the carton labeling of multiple products include bolding, boxing, and varying fonts.

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.[35] Based on these discussions, FDA recommends the following.

a. Color differentiation

Color differentiation is a tool that may help: (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 or cautionary statements. When applying

[34] ISMP, "Safety Briefs: How Colorful Is Too Colorful When It Comes to Patient Safety? Will Color-Tinted IV Tubing Help?," *ISMP Medication Safety Alert! Acute Care*, 14(15): 2009, 1–2.

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

color, sponsors should ensure that the text highlighted by the color has adequate color contrast against the background color.

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 generally reserved for special circumstances or after the appropriate human factor testing data or information has been received and evaluated by FDA before use.

The use of color coding on drug labels has been limited and has its own risks. 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, user-applied color-coded labels in the operating room). One example is color coding the caps used for ophthalmic products to distinguish a therapeutic class (e.g., beta-blockers having 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, color coding has made it difficult for 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 should be limited to the cap color.

Certain applications of color coding may be appropriate. Examples include the color coding of certain drug product strengths, such as warfarin, levothyroxine, and conjugated estrogen-containing products where the colors of the strengths are universally color coded across all manufacturers.

F. There Should Be Consistency Between the Container Label and Carton Labeling and Other Approved Labeling

When product information is presented inconsistently among container labels, carton labeling, and other approved labeling, this can lead to confusion that can result in medication errors. Information that appears on the container label or carton labeling, on FDA-approved patient labeling, and in the PI should be consistent.[36] Sponsors should pay attention to how critical product information is conveyed across all approved labeling (e.g., product name(s), dosage

[36] There may be some acceptable differences between the recommended presentation of product information in the product title in Highlights of Prescribing Information and the carton labeling and container label. See FDA draft guidance for industry *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products—Content and Format* (January 2018). When final, this guidance will represent the FDA's current thinking on this topic.

form(s), strength(s), route(s) of administration, warnings or cautionary statements, controlled substance schedule). Additionally, package type terms should be consistent across all approved labeling.[37] Furthermore, dosage terminology on the container label and carton labeling should be consistent with the dosage terminology in the PI. Given that the recommended dosage is required in the DOSAGE AND ADMINISTRATION section for products with labeling in Physician Labeling Rule format,[38] and given that there may be a difference between the recommended dosage and the usual dosage of a product, the PI, container label, and carton labeling for such products should use consistent dosage terminology (i.e., *recommended dosage* or *dosage* if there is limited space) and avoid the terminology *usual dosage*.

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. For drugs, the proprietary name and established or proper name must be displayed in a manner consistent with FDA regulations, taking into account all pertinent factors, including typography, layout, contrast, and other printing features (see § 201.10(g)(2); for biological products, the proper name must be displayed consistent with § 610.60 and 21 CFR 610.61; for requirements applicable to biological products that do not fall within the specified categories of biological products described in § 601.2 (21 CFR 601.2) (non-specified biological products), see § 610.62).[39]

For **fixed-combination drug products**[40], the word *and* along with commas (for products with greater than two drug substances) should be used to separate drug substances in the established name per USP nomenclature.[41] For example:

- Drugozide and Drugomycin Tablets
- Drugozide, Drugomycin, and Drugazole Capsules

The established name for drug products should be displayed with the finished dosage form. If space does not permit the finished dosage form to appear on the same line as the active

[37] See (1) FDA guidance for industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018) and (2) USP General Chapter <659>, Packaging and Storage Requirements.

[38] See 21 CFR 201.57(c)(3).

[39] For non-specified biological products, the regulations provide more specific requirements for the position and prominence of the proper name and the legibility of information on the package and container label.

[40] Here we refer to drugs submitted for approval or approved under section 505 of the FD&C Act (21 U.S.C. 355).

[41] The FD&C Act recognizes USP as the official compendia; thus, labels for drug products should be based upon these standards.

ingredient, we recommend placing the finished dosage form on the next line below the drug component of the established name.

Tradename (drugozide injection)	or	Tradename (drugozide) injection	or	Tradename (drugozide) Injection

For biological products, the proper name should not include the finished dosage form. However, if the finished dosage form is included on the carton or container label, the finished dosage form may appear on the line below the proper name or proprietary name to distinguish the proper name from the finished dosage form. For example:

Specified biological products[42]	Non-specified biological products
Tradename (drugimab-cznm) Injection	drugimab-cznm Tradename Injection

Alternatively, the finished dosage form can appear on the same line as the proper name if the proper name is enclosed by parentheses to distinguish it from the finished dosage form. For example:

Tradename
(drugimab-cznm) injection

B. Tall Man Lettering

Tall man lettering on approved container labels and carton labeling can sometimes be used to help distinguish similar-looking name pairs that have been confused postmarket. Dissimilar letters in each of the names are placed in uppercase letters to bring attention to the point of dissimilarity between the names of concern (e.g., drugOZide versus drugEXide). Despite the use of tall man lettering, sometimes the dissimilar letters can still be overlooked. In cases where sponsors are concerned that tall man lettering alone will be insufficient to distinguish similar-looking name pairs, sponsors can consider additional approaches (e.g., larger font, boldface type, color highlighting). We recommend that sponsors consult FDA before using this technique and supply information concerning the postmarket confusion, a description of how the tall man letter string was selected, and data demonstrating that the proposed presentation will adequately distinguish between the potentially confusing product names. A list of approved established name pairs that use tall man lettering can be found on the FDA Name Differentiation Project web page at https://www.fda.gov/drugs/medication-errors-related-cder-regulated-drug-products/fda-name-differentiation-project.

C. Product Strength

[42] § 601.2(a).

A product's strength is critically important information for the end user. If the product strength is not clearly displayed on the container label or carton labeling, or if it is expressed in units of measure that are incongruent with those used in the DOSAGE AND ADMINISTRATION section of the PI, the wrong strength can be selected or the wrong dose administered (i.e., overdosing or underdosing). Sponsors should consider whether the product's strength is visible when the product will be placed on a pharmacy shelf. We recommend the following measures to avoid or minimize commonly reported dosing errors.

1. Strength Differentiation

Product selection errors leading to underdosing or overdosing 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 (see also section III.E.2 for a discussion on the use of color), among others.

2. Strength Designation

Product strength designations should include a unit of measure and use that unit of measure consistently across all elements of the labeling (e.g., container, carton, FDA-approved patient labeling, PI). The product strength should match the units of measure described in the DOSAGE AND ADMINISTRATION section of the PI to avoid error. For example, confusion and dosing errors can occur if product strength is expressed on the container label in percentage, but the strength of the drug is expressed in milligrams in the DOSAGE AND ADMINISTRATION section or the Instructions for Use.

Sponsors also should use the same units of measure across products that contain the same active ingredient (e.g., use *mg* for milligram to express the strength for all nitroglycerin products, rather than using *mg* for one nitroglycerin product and *mcg for another nitroglycerin product*).

For solid oral dosage forms, there may be circumstances where the milligram amount of drug per single unit (e.g., tablet, capsule) should be expressed to avoid confusion as to how much product is contained in a single unit compared to the total contents of the entire container. This generally applies to containers that hold a small net quantity of product (e.g., five or fewer tablets). There may be a risk of confusion if an end user misinterprets the strength and believes the entire contents of a container should be administered to achieve the end user's dose. For example, a dosing card that contains three-100 mg tablets should specify that the strength is *100 mg per tablet* as opposed to simply stating 100 mg.

3. Small-Volume Injection Products

For **small-volume injection** products, the product strength should be expressed as the quantity per total volume followed by the quantity per milliliter (mL), as described in USP General

Chapter <7>, Labeling.[43] A number of overdoses have occurred with small-volume injection products because of health care practitioner or patient confusion when determining the quantity of drug in the container. In most cases, the user noticed the quantity per milliliter or 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 the administration of the entire contents of a container, when only a portion of the total volume was needed.

To avoid such confusion, the quantity per total volume should be the primary and prominent expression on the PDP of the label, followed in close proximity by quantity 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 not 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 underdosing. For containers holding a volume of less than 1 mL, the quantity per fraction of a milliliter should be the only expression of strength. The following is an example for contents less than 1 mL:

12.5 mg/0.625 mL
or
12.5 mg per 0.625 mL

If a product contains a volume equal to 1 mL, then the quantity per single mL should be expressed as mg/mL, not mg/1 mL. For example:

5 mg/mL

For single-dose combination products with an autoinjector device constituent part, where the entire content is administered and there is no possibility of administering a partial dose, the expression of strength should only include the quantity per total volume (not the quantity per milliliter). For example:

150 mg/1.5 mL

a. Exceptions to strength expression for small-volume injection products

The following are exceptions to expressing strength as quantity per total volume. In certain cases, the primary and prominent expression of quantity per total volume would not be effective in preventing medication errors.

[43] Specifically, Labels and Labeling for Injectable Products and Quantity and Total Volume for Injectable Drug Products Packaged in Single- and Multiple-Dose Containers.

- For insulin products, generally the only expression of strength should be the quantity in units per milliliter because only a portion of the supplied total volume is typically administered at a time. The expression of quantity per total volume should be omitted because it would be inconsistent with administered amounts and could result in potential medication errors. The following is an example of how strength should be expressed for insulin products:

  100 units/mL (U-100)

- For drug products that are ordered and administered by percentage strength (e.g., drug products for local anesthesia), there should be 3 expressions of strength when the total volume is greater than 1 mL (i.e., percentage strength, quantity per total volume, and quantity per milliliter). For example:

  1%
  (100 mg/10 mL)
  (10 mg/mL)

4. Expression of Strength for Dry Solid Injectable Products Requiring Reconstitution

Dry solid injectable products requiring reconstitution should express the strength in terms of the quantity of drug per vial as follows:

XX mg/vial or XX mg per vial

Instructions for reconstituting the product, resultant concentration, and storage conditions should be included on the vial container label, if space permits, and carton labeling. These instructions will inform end users responsible for preparing the product of the name and volume of diluent to be used for reconstitution, the amount of drug contained in each milliliter (concentration) once reconstituted, and storage requirements for the reconstituted product (see section IV.F.2 Beyond-Use Dates).

5. Expression of Strength for Dry Solid Oral Products Requiring Reconstitution

Dry solid oral products requiring reconstitution should express the strength of the concentration after the diluent is added in terms of the quantity of drug in each mL or quantity per 5 mL (if the recommended dose is 5 mL).

Instructions for reconstituting the product, resultant concentration, and storage conditions should be included on the container label and carton labeling. These instructions will inform end users responsible for preparing the product of the name and volume of diluent to be used for reconstitution, quantity of drug contained in each milliliter (concentration) or quantity per 5 mL once reconstituted, and the storage requirements for the reconstituted product (see section IV.F.2 Beyond-Use Dates).

6. Fixed-combination Drug Products

For fixed-combination drug products, slashes should be used to separate the strength of each ingredient on the container label and carton labeling.

Drugozide and Drugomycin Tablets
100 mg/250 mg

Drugozide, Drugomycin, and Drugazole Capsules
100 mg/250 mg/40 mg

7. Salt Nomenclature

When a product contains an active ingredient that is a salt, the USP Salt Policy[44] may apply when naming and labeling the drug product.[45]

8. Prodrugs

For **prodrugs**, the product strength should be expressed in terms of the established or proper name of the prodrug. For example, Fosaprepitant for Injection is a prodrug for aprepitant. After administration, fosaprepitant is converted to aprepitant. The strength of this product is based on fosaprepitant rather than aprepitant.

9. Metric Measurements

The dose and expression of strength should appear in metric units of measure, such as *mL*, *mg*, and *mcg*, rather than household or apothecary measurements (e.g., teaspoon, tablespoon, drams, grains) or ratios. For single-entity injectable products (i.e., containing a single active ingredient), the strength should be expressed in metric units (not a ratio). For example, Epinephrine Injection, USP, 1:1,000 should be expressed as 1 mg/mL (see also section IV.C.3 above).[46]

Fatal errors have occurred when health care providers or patients have miscalculated medication doses when converting from one unit of measure to another (for example, the recommended 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).

[44] For implementation of this policy, see FDA guidance for industry *Naming of Drug Products Containing Salt Drug Substances* (June 2015).

[45] USP General Chapter <1121>, Nomenclature.

[46] See the Single Entity Injectable Drug Products web page at https://www.fda.gov/drugs/information-drug-class/single-entity-injectable-drug-products and USP General Chapter <7>, Labeling.

10. Location of Net Quantity of Contents Statements

Product selection or dosing errors can occur if the net quantity is mistaken for the product strength, leading to underdosing or overdosing. 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. Generally, the net quantity should appear on the PDP, but should be separate from and less prominent than the strength (e.g., not highlighted, boxed, or bolded).

11. Leading and Trailing 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 trailing zero (e.g., 4 mg, not 4.0 mg). Conversely, decimal numbers smaller than 1 should always be preceded by a 0 (e.g., 0.4 mg, not .4 mg). This serves to enhance the visibility of the decimal point.

Commas should be used for strength and dosing numbers of 1,000 and above to improve the readability of larger numerals.[47]

Decimals are often marked with commas in Europe and many other countries. However, the use of a comma in place of a decimal (i.e., decimal commas) is not commonly used in the United States, and has led to confusion and medication errors.[48] The labels and labeling of products intended for use in the United States should use decimal points and not decimal commas.

D. Route(s) of Administration

The route(s) of administration should generally 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 generally be avoided because it is easy to overlook the word *not*, even when it is emphasized by uppercase, bolding, underlining, or other means. If a negative statement is unavoidable, it should follow an affirmative statement. Using affirmative statements helps to ensure that end users understand the intended route(s) of administration, even if they do not read every word.[49, 50, 51]

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[47] The ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations, 2010, http://www.ismp.org/tools/errorproneabbreviations.pdf.

[48] Cohen, M., and Smetzer, J., "Decimal Commas Are a Problem," *Hospital Pharmacy*, 49(8), 2014, p. 689–691.

[49] Eastman Kodak Company, *Ergonomic Design for People at Work*, 2nd edition, Chengalur, S. N. et al., eds., Hoboken, NJ: John Wiley & Sons, 2004.

[50] Wogalter, M. S., ed., *Handbook of Warnings*, Mahwah, NJ: Lawrence Erlbaum Associates, 2006.

[51] Proctor, R. W., and Vu, K. L., *Handbook of Human Factors in Web Design*, Abingdon, UK: Routledge, 2005.

1. Products Intended for Otic or Ophthalmic Administration

Confusion between products intended for otic and ophthalmic administration can result in choosing the wrong route of administration. The confusion can be related to similar packaging and container closures used for the products, as well as the use of the words *otic* and *ophthalmic*, which may be unfamiliar to consumers. To minimize such errors, the container labels and carton labeling for these products should include a prominent graphic (e.g., picture of an ear, picture of an eye) and statement (e.g., *For use in ears only*, *For eye use only*) to help convey the intended route of administration.

E. Warning or Cautionary Statement(s)

When warning(s) or cautionary statement(s) are added to the container label or carton labeling, they should generally be written affirmatively. Non-affirmative warning or cautionary statements have been misinterpreted. 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.

1. Neuromuscular Blocking Agents

All injectable neuromuscular blocking agents (NMBAs) and paralyzing agents must be packaged in vials with a cautionary statement printed on the ferrules and cap overseals.[52] The container label and carton labeling for NMBAs should state *WARNING: Paralyzing Agent* in red, bold font on the PDP. The warning should be placed on the line directly under the listed strength. To accommodate this addition, other information, such as the manufacturer name and logo, can be moved from the PDP to the side panel, if necessary. An additional warning statement should be displayed in red, bold font on the side panel:

> WARNING: Paralyzing Agent. Causes Respiratory Arrest. Facilities must be immediately available for artificial respiration.

NMBAs produce muscle paralysis (including the muscles associated with breathing) and can cause significant patient harm, including death, when used in error. Wrong-drug errors, particularly when an NMBA is inadvertently administered instead of an intended non-NMBA, are of particular concern because NMBAs should be used only if facilities for intubation, mechanical ventilation, oxygen therapy, and an antagonist are immediately available.

F. Expiration Dates and Beyond-Use Dates

1. Expiration Dates

Manufacturers have used various ways to express the expiration date on container labels and carton labeling, such as expressing the expiration date with the month and day or the month and

[52] For additional requirements for NMBA cap overseals and ferrules, see USP General Chapter <7>, Labeling.

year. The use of abbreviations such as 2-letter months and 2-digit years (e.g., MA12) 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.

If the term *expiration date* is abbreviated on the container label or carton labeling, it should be done in a clear and understandable manner. FDA recommends using one of the following abbreviations for expiration date:

Table 1: Examples of Abbreviations for Expiration Date

Examples of Abbreviations for Expiration Date
EXP.
EXP
EXPIRY
EXP DATE
Exp. Date

We believe that these abbreviations are readily distinguished and understood by readers to mean *expiration date*.

FDA recommends that the expiration date on the container label or carton labeling include a 4-digit year, month, and day in YYYY-MM-DD format (e.g., 2021-01-01) if using only numerical characters or in YYYY-MMM-DD format (e.g., 2021-JAN-01) if using alphabetical characters to represent the month. If there are space limitations on the container label or carton labeling, the text may include only a 4-digit year and month, expressed as YYYY-MM (e.g., 2021-01) if using only numerical characters or YYYY-MMM (e.g., 2021-JAN) if using alphabetical characters to represent the month. FDA recommends using a hyphen or forward slash to separate the portions of the expiration date.

In situations where the expiration date includes only a year and month due to space limitations, FDA considers the drug product's actual expiration date to be the last calendar day of the month that is included in the expiration date on the container label or carton labeling.[53] For example, an expiration date of 2021-07 (or 2021-JUL) would be interpreted by FDA to mean that the drug expires on July 31, 2021.

2. Beyond-Use Dates

The beyond-use date (BUD) is the date or time beyond which a drug product, that has been manipulated (e.g., reconstituted, diluted, initial entry of a multiple-dose vial, change in storage conditions from refrigerator to controlled room temperature storage) in some fashion that affects the product's quality characteristics (i.e., sterility, strength, and purity), must be discarded. The time period for establishing the BUD should be identified in the labeling (e.g., Discard after 28 days). The BUD should not be later than the manufacturer expiration date that appears on the container label.

[53] For more information on expiration dating, see USP General Chapter <7>, Labeling.

We recommend that sponsors consider including a space for end users to write in the BUD (e.g., Discard after ___/___/___ Time_____) for drug products.

G. Barcodes[54]

For some drug products, a linear barcode consisting of, at a minimum, the National Drug Code (NDC) must be placed on the immediate container label and carton labeling of all drug products (§ 201.25(b)). Where required, the linear barcode must appear on the drug's label as defined by section 201(k) of the FD&C Act (21 U.S.C. 321(k)), meaning the linear barcode must be on the outside container or wrapper, as well as on the immediate container, unless the barcode is easily legible through the outside container or wrapper. We recommend that drug products not subject to this requirement nonetheless include this information in the same manner. Linear barcodes allow health care professionals to use barcode scanning equipment to verify that the right drug (at the right dose and via the right route of administration) is being given to the right patient at the right time. This can help reduce the number of medication errors that occur in hospitals and health care settings.[55]

Where required, the linear barcode must be surrounded by sufficient blank space to allow scanners to read the barcode properly (see § 201.25(c)(2)). We recommend that this approach be followed for all drug products. Cases have been reported of linear barcodes being positioned too close to other barcodes used during the manufacturing process or barcodes being printed on transparent or translucent backgrounds, which has led to difficulty scanning and reading the barcode properly; thus, we recommend locating the linear barcode away from other barcodes and ensuring there is adequate contrast between the background color and the barcode to allow for proper scanning (e.g., print the barcode in dark ink on a white background). The linear barcode should be placed in a conspicuous location 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). Sponsors should also consider the curvature of the container on which the barcode will be placed because extreme curvature may distort the linear barcode and impede scanning. In these cases, placement of the barcode in a vertical, as opposed to horizontal, orientation should be considered.

A manufacturer or repackager may voluntarily put a two-dimensional data matrix barcode on all levels of packaging, including the immediate container, as long as the product remains compliant with all other labeling requirements, including the linear barcode requirements under § 201.25.

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[54] Although not included in this guidance discussion, we remind sponsors that the product identifier, including a two-dimensional data matrix barcode, is required under section 582 of the FD&C Act, as amended by the Drug Supply Chain Security Act, for packages and homogenous cases of certain drug products to facilitate the tracing of product through the pharmaceutical distribution supply chain. For more information, see FDA guidance for industry *Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers* (June 2021).

[55] See FDA guidance for industry *Bar Code Label Requirements Questions and Answers* on the FDA Bar Code Label Requirements web page at https://www.fda.gov/vaccines-blood-biologics/advertising-labeling-biologics/bar-code-label-requirements.

H. National Drug Code Numbers

The NDC, which is a unique numerical identifier assigned to drug products, consists of a series of digits divided into 3 segments (labeler code, product code, and package code).[56, 57, 58, 59] The NDC is widely used in the United States by consumers, health care providers, researchers, industry, and regulators for the purpose of identification and verification and is linked to crucial information about the drug, such as drug name, strength, formulation, packaging, and the company that markets the drug in the United States. As such, FDA strongly encourages sponsors to include the NDC on all drug labels.

The second segment of the NDC is referred to as the *product code*. A separate, unique product code is required for, among other things, each strength, dosage form, or product characteristic (e.g., shape, color, imprint, scoring, flavor) of a drug.[60] Drug products that contain the same concentration of active ingredient(s) but are available in different strengths or deliver different doses must use different product codes. 21 CFR § 207.37. For example, injectable products may be available in different strengths (e.g., 20 mg/2 ml, 40 mg/4 ml) even though they are the same concentration (e.g., 10 mg/ml). Another example is when injectable products contain the same total volume and the same total quantity per total volume but deliver different doses. For instance, a combination product might be marketed in two different prefilled pen injector presentations, each with a total volume of 3 ml and a strength of 30 mg/3 mL (concentration of 10 mg/mL). However, one pen injector might deliver 6 doses of 5 mg/0.5 ml, and the other might deliver 3 doses of 10 mg per 1 ml.

The similarity of the product code numbers has led to the selection and dispensing of the wrong strength and wrong drug. The product code is often used by health care providers to confirm the correct product and strength. The assignment of sequential numbers for the product code (e.g., 6666, 6667, and 6668) has not been an effective differentiating feature and, therefore, is not recommended.

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[56] Under section 510 of the FD&C Act (21 U.S.C. 360), as amended, and part 207 (21 CFR part 207), 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 section 510(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 (section 510(j)(1)) (see also § 207.17 and § 207.45). 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 (section 510(j)(2); § 207.57). Pursuant to section 510(e), FDA may assign an NDC as the listing number for each drug listed pursuant to section 510(j), and FDA makes such assignments pursuant to § 207.33(c) and (d).

[57] Information regarding FDA's drug registration and listing is available on FDA's Drug Registration and Listing System web site at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/DrugRegistrationandListing/default.htm.

[58] See § 207.33(b) for specific format requirements.

[59] Information regarding FDA's NDC Directory is available on FDA's National Drug Code Directory web site at http://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm.

[60] See § 207.35.

If for some reason the numbers in the middle segment are similar, increasing the prominence by increasing their size in comparison to the remaining digits in the NDC number or putting them in bold type may help to minimize the risk for medication error (e.g., xxxx-**XXXX**-xx).

The reuse of an NDC for a different drug than the drug for which the NDC has been assigned is prohibited (§ 207.37(a)(1)). Because the reuse of NDCs has led to the dispensing and administration of the wrong drug or wrong strength, the practice is no longer permitted for new products.

I. 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. 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. 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 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 unit dose blisters may be torn apart, punctured, or separated from the outer carton by the end user. Therefore, FDA recommends the following when developing the container label and carton labeling for blister pack presentations.

1. Unit Dose Blister Cell Label

For products where each blister cell has a label, the barcode and other required or critical information (e.g., proprietary and established or proper name, dosage form,[61] strength, lot number, expiration date, 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. The barcode, when required, must remain intact under normal conditions of use (see 21 CFR 201.25(c); thus, the barcode (and other required or critical information) should not be printed across the perforations of a blister pack. Sponsors should include only one dosage unit per blister (e.g., one tablet, one capsule).

[61] Established names for drug products typically include the dosage form. We include dosage form here because proper names for biological products typically do not include a dosage form.

2. Product Strength on Carton Labeling

The product strength on the PDP 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 compared to the total contents of the entire blister pack. We recommend the following:

XX mg per tablet or XX mg per capsule

For products where a blister pack or carton contains 1 dose, if the total dose requires more than 1 unit (e.g., 1 tablet), then the PDP should display both the milligram amount of drug per single unit (e.g., tablet, capsule) and the total dose contained in the blister pack or carton (e.g., contains 40 mg total dose (2 x 20 mg tablets)). In some cases, the total dose should appear more prominently than the strength per unit on the PDP if there is a risk that users will only administer one unit believing it is the full dose.

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. Additionally, the ability to scan barcodes may also be impaired when they are printed on foil. When possible, a nonreflective material should be used to enhance the readability of product information.

4. Blister Pack Label Design

Thoughtful usage of blister packs or calendar packs that can be dispensed intact to patients may help to reduce medication errors. Blister packs may improve patient adherence and minimize the risk of accidental exposure to the drug. Additionally, blister packs can be designed so that critical information stays with the medication throughout the intended use of the product by the end user. However, 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 ensure that the packaging configuration makes sense for the dosage and administration of the drug product and the intended patient population. If multiple configurations of blister packs will be introduced, sponsors should ensure there is adequate differentiation between them and adequate mechanisms to ensure they can be easily distinguished and correctly selected throughout the medication use process (e.g., prescribing, dispensing). Blister pack label design factors that have been associated with reported medication errors include the following:

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

- Labeling doses in the package with fixed days of the week when the dosage and administration do not require such sequencing. For example, a packaging configuration labeled with the days of the week (e.g., Mon., Tues., Wed.) can lead to delays in starting therapy because patients may 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 keeping records of controlled substances in facilities, the number has been confused for the tablet strength and day of the month.

- Providing more doses than needed for a single course of treatment, leading to an 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 the location of ferrules and caps of medication vials, the information provided on them has a critical role in providing crucial information to the health care provider and should be limited to important safety messages critical for the prevention of imminent, life-threatening situations. For some products, a cautionary statement is required to be included on ferrules or caps; if no cautionary statement is required, the top surface of the vial, including the ferrule and cap overseal, should remain blank.[62] 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.

USP General Chapter <7>, Labeling, contains a section entitled Ferrules and Cap Overseals. Sponsors should conform with the additional recommendations set forth in USP General Chapter <7>.

C. Color Closure System for Concentrated Potassium Chloride

A black closure system on a vial (e.g., a black cap overseal and a black ferrule to hold the elastomeric closure) or a black band or series of bands above the constriction on an ampule are used only for Potassium Chloride for Injection Concentrate.[63] 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.[64] As such, black cap overseals/ferrules/lines should not be used on any other drug product.

[62] See USP General Chapter <7>, Labeling, Ferrules and Cap Overseals
[63] USP General Chapter <7>, Labeling
[64] For more information, see USP General Chapter <7>, Labeling.

D. Labels and Labeling for Large-Volume Injections

FDA receives many reports of confusion and errors involving **large-volume injections**. These reports cite look-alike container labels, lack of prominence of important information on a label, and label clutter. The container labels and carton labeling for large-volume injections must align with applicable USP standards and FDA regulations.[65]

1. Information for Container Labels of Large-Volume Injections

Based on information and recommendations from a joint public meeting held by FDA, ISMP, and USP in 2007[66] as well as postmarketing experience, the following information includes required elements as well as recommendations for information that should be on container labels of large-volume injections:

- Product name(s) (see section III.C)
- Package type term
- Primary expression of strength is total quantity per total volume, followed by quantity per milliliter (see sections III.C and IV.C.3)[67]
- The statement *Each 100 mL contains . . .*
- Linear barcode (see section IV.F)
- Product identifier, when applicable (see section IV.G)
- NDC (see section IV.H)
- Lot number (21 CFR 201.18)
- Expiration date (21 CFR 201.17)
- The statement *Sterile*
- General and/or special storage requirements, such as:

[65] See USP General Chapter <7>, Labeling, for USP standards. See FDA regulations in 21 CFR part 201 for drugs; and FDA regulations in 21 CFR part 610, Subpart G, Labeling Standards, for biological products.

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

[67] Use when a large-volume parenteral contains a drug (e.g., Dopamine, Esmolol) in addition to the infusion solution (e.g., Dextrose Injection 5%). For strength expressions for electrolytes, see USP General Chapter <7>, Labeling.

  - *See USP Controlled Room Temperature*
  - *Protect from Freezing* should only be used if the drug product is adversely affected by freezing[68]

- Labels of ports (e.g., arrows with *med* or *set*)
- The statement *Do not add supplementary . . . to the Y port . . .*
- The statement *Additive compatibility, consult pharmacist*
- Recycling code symbol
- Warnings (if any) or cautionary statements (if any) (e.g., central line only)
- Name and place of the manufacturer
- The statement *For use only with a calibrated infusion device*
- A statement of dosage, such as *See prescribing information*

2. Container Label Clutter

To help mitigate confusion and errors involving large-volume injections, the container labels should be devoid of clutter, prominently state important information, and be adequately differentiated from other products. Unless otherwise required (e.g., by USP) or unless space permits, in order to avoid detracting from important information for the safe use of the product, we recommend against including the following information on the container label for large-volume injections:

(1) All secondary trademark information (e.g., proprietary names for containers/packaging material)

(2) Symbols

(3) Statements such as *Caution—Check for minute leaks by squeezing container firmly . . .* and *If leaks are found . . .*

(4) The statement *Use only if solution is clear and container is undamaged*

(5) Statements about *series connection*

(6) An osmolarity statement (except as required under USP monographs for specific products)

[68] USP General Chapter <7>, Labeling.

(7) A lactic acidosis statement (except as required by USP on lactated Ringer's bags)

(8) Statements such as *Printed in USA*

(9) Statements such as *Dose intravenously as directed by the prescriber*

(10) The statement *Whenever possible use central route*

(11) A pH statement

(12) A blood transfusion warning

(13) Statements such as *non-pyrogenic*

(14) Warnings or cautionary statements for purposes of interstate commerce, except those that are necessary for compliance with provisions of the law

3. Other Container Label and Carton Labeling Considerations

Sponsors should consider the following labeling aspects for container labels for large-volume injections:

(1) If the overwrap for a large-volume injection is nontransparent (e.g., opaque, made of foil), then the overwrap should contain the same information as the container label (e.g., product name, strength, lot number, expiration date, barcode, NDC, product identifier (if applicable)).

(2) Sterile Water for Injection is intended only for use as a diluent for drugs intended for parenteral injection. FDA has received medication error reports[69] that describe patients who were accidentally administered only Sterile Water for Injection. To avoid these errors, we recommend including a statement on the container label and the overwrap to convey that Sterile Water for Injection is intended for use only as a diluent, and consider including a statement that cautions against direct intravenous administration.[70]

(3) Avoid abbreviations of salts when used at the beginning of a product name to avoid misinterpretations. For example, the abbreviation *Na Salicylate* to abbreviate Sodium Salicylate should be avoided. However, the abbreviation *HCl* for hydrochloride at the end of a name does not raise concerns.

4. Product Differentiation

[69] See FDA Patient Safety News #15, May 2003, at https://archive.org/details/gov.ntis.ava21204vnb1.

[70] See also the USP monograph for Sterile Water for Injection.

Product selection errors can occur when similar-appearing large-volume injections are stored or displayed in close proximity to each other or stored near other products that are packaged in similarly large containers. Sponsors should ensure there are elements in the labels and labeling to help differentiate different products and bring attention to important differences. Sponsors can consider applying label and labeling techniques, such as the use of boxing, prominent typeface or type weight, and color, as appropriate.

(1) For large-volume injections with the same active ingredient as other products and that are packaged in similarly large containers but intended for different routes of administration (e.g., Sodium Chloride Injection versus Sodium Chloride Irrigation), the difference in routes of administration should be prominent on the container label and carton labeling.

(2) For hypertonic Sodium Chloride Injection, sponsors should ensure that the words *Hypertonic Sodium Chloride* are prominent on the container label and carton labeling.

(3) For large-volume solutions intended for dialysis, hemofiltration, or irrigation, the container label should prominently state the intended route of administration (e.g., for irrigation only), and consider including a statement indicating that the product is not intended for use intravenously or intra-arterially following the affirmative statement.[71]

E. Transferable or Peel-off Labels for Injectable Medications

Currently, once an injectable medication is withdrawn from the commercial container closure (e.g., vial, ampule) into a syringe for administration, the syringe, if not appropriately labeled, does not provide information needed by the end user to verify the drug name(s) and strength before administration. Such unlabeled medication is unidentifiable, and this has led to administration of the wrong drug and wrong strength in perioperative and other procedural settings. Having appropriate labeling addresses a risk point in the administration of medications.[72]

FDA recommends that sponsors develop, when appropriate, a transferable or peel-off label for the commercial containers of single-dose and multiple-dose injectable products that may be used in perioperative and other procedural settings. This type of label can help to minimize the use of unlabeled syringes and can be affixed to an unlabeled syringe after the medication is withdrawn from the commercial container closure, and the label should contain sufficient information to identify the contents of the syringe. The transferable or peel-off label should not overlay or cover important information on the product label, such as the total quantity per total volume. Furthermore, if the product is intended for use in a sterile field, sponsors should ensure that the transferable or peel-off label is sterile. As an alternative to transferable or peel-off labels, the sponsor can consider providing labels that identify the drug name(s) and strength on a separate sheet within the carton.

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[71] For more information, see USP General Chapter <7>, Labeling, for USP standards.

[72] The Joint Commission, "National Patient Safety Goals Effective January 2017," January 2017, https://www.jointcommission.org/assets/1/6/NPSG_Chapter_HAP_Jan2017.pdf.

F. Double-Sided Container Labels and Carton 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 printing on both the front and back panels, the critical information should be repeated on each side. As previously noted, double-sided printing on clear, transparent, or translucent labels and carton labeling has contributed to medication errors. When double-sided printing is used on clear, transparent, or translucent labels and carton labeling, such as low-density polyethylene ampules 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 PDP following the expression of strength. This statement can be made more prominent by using boldface type, large-size type, or a contrasting color.

A PBP contains many single doses; therefore, the product will typically have a BUD after initial entry or reconstitution that differs from the expiration date of the product. We recommend that the PBP container labels bear a statement describing the time frame in which the container may be used once it has been entered (e.g., Discard contents within 4 hours after initial entry). Sponsors can also consider providing labels on which the end user can write the BUD and beyond-use time, and then affix it to the container.

H. Communication of Important Product Changes

Changes to marketed products, such as new strength(s), formulation, certain inactive ingredients, or product appearance, can be communicated to health practitioners on the container label, if space permits, and on the carton labeling. For example, a change in product strength can be communicated as *New Strength* or *Note New Strength*. If included, this statement should be printed on the PDP, after approval of the change, for a limited manufacturing period of time (e.g., 6–12 months).

I. Dosing Devices for Oral Liquid Drug Products

Dosing devices included with an oral liquid drug product should be appropriate for the dosages to be measured.[73] The dosing device should deliver an oral liquid drug product (e.g., solution, suspension) in a volumetric unit of measure consistent with recommended dosing. Metric units (e.g., mL) should be the standard unit of measure used on prescription container labels for oral liquid drug products; thus, dosing devices for oral liquid drug products should also use metric units (e.g., mL) for measure markings. For example, sponsors should create an oral syringe that is calibrated in milliliters rather than milligrams. Measure markings should be congruent with

[73] FDA guidance for industry *Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products* (May 2011) addresses issues concerning dosing devices for over-the-counter liquid drug products.

the DOSAGE AND ADMINISTRATION section of the PI. Additionally, there should not be any unnecessary markings on the dosing device that are not referred to in the product's labeled dosage directions. We recommend that all dosing devices for oral liquid drug products include a statement similar to *For Oral Administration Only* or *For Oral Use Only*.

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))). Product samples are typically packaged in small containers. For this reason, at a minimum, product sample labels for drugs must also include the proprietary (if any) and established names; dosage form;[74] lot number or control number; and name of the manufacturer, packer, or distributor of the drug (§ 201.10(i)). For biological samples, labels must include the proper or common name, lot number or other lot identification, manufacturer name, and the recommended individual dose for multiple-dose containers (§ 610.60(c) and (d)). We also strongly encourage including the expiration date and product strength. Product samples are required to be listed;[75] thus, they are assigned an NDC. Although the NDC is not required to be on the labels of samples, we recommend including it on the labels of samples to allow for product identification. Professional samples packaged as packs or kits should not be labeled with terms such as *starter*, *starter samples*, or *patient starter pack*.[76] 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's name and specific instructions for use.

For solid oral dosage forms, there may be circumstances where the strength should be expressed as milligram amount of drug per single unit (e.g., XX mg per tablet) so that there is no confusion as to how much product is contained in a single unit compared to the total contents of the entire container. We recommend the following:

XX mg per tablet or XX mg per capsule

This generally applies to product sample containers that hold a small net quantity of product (e.g., five tablets or less) which the patient is only supposed to take one dosage unit at a time. In this case, the risk is that the end user will misinterpret the strength and take the entire contents of the container to achieve the prescribed dose.

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[74] Established names for drug products typically include the dosage form. We include dosage form here because proper names for biological products typically do not include a dosage form (see 21 CFR 610.60(c) and (d)), however, we encourage inclusion of dosage form when space permits.

[75] Information regarding FDA's drug registration and listing is available on FDA's Drug Registration and Listing System web site at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/DrugRegistrationandListing/default.htm.

[76] See the final rule *Prescription Drug Marketing Act of 1987; Prescription Drug Amendments of 1992; Policies, Requirements, and Administrative Policies*, published December 3, 1999 (64 FR 67720 at 67742).

K. Package Type[77]

For injectable drugs for parenteral administration, the inclusion of the **package type** term on container labels and carton labeling (e.g., single-dose, multiple-dose, single-patient-use, PBP, imaging bulk package) is important in situations where it is unclear how the medication should be safely handled and used by simply viewing the container. For example, sponsors are generally required to include the term *single-dose*[78] on vials that contain a specific quantity of a drug product intended to be used as a single injection/infusion on a single patient to differentiate it from a multiple-dose vial and alert the user to the appropriate use of the product.

L. Insulin Pens

Insulin pens are intended to be used for a single patient. The reuse of insulin pens on multiple patients can result in exposure to bloodborne pathogens. To mitigate potential exposure errors, the safety warning *For Single Patient Use Only* should be placed immediately below the product strength so that there is no intervening matter between the product strength and the warning.[79] This will ensure that the warning is in the same viewing angle and field as the product name(s) and strength, and that it is less likely to be overlooked as a result. In addition, we recommend using red-shaded and bolded letters in a contrasting colored box to enhance visibility and prominence.

M. Quick Response Code

A Quick Response (QR) code is a type of matrix barcode (or two-dimensional barcode) that can be read by a mobile phone. A QR code is not required to be included on the product labeling and does not contain the information that is required under section 582(b)(2)(A) and (e)(2) of the FD&C Act. QR codes may provide various bits of information (e.g., internet address, phone number). FDA has not developed a formal position on the use of QR codes at the time of publication of this guidance and will review proposals to include such codes on a case-by-case basis. If a manufacturer chooses to include a QR code, we recommend that it appear on the side or back panel of the container label or carton labeling, away from the barcode and in a size that does not compete with or distract from the presentation of other required or recommended information on the label or labeling.

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[77] For more information, USP General Chapter <659>, Packaging and Storage Requirements, includes package type terms and definitions.

[78] The package type term "single-dose" is required to appear on the container labels of single-dose injectable medical products that have a USP monograph, when space permits (FD&C Act section 502(g) (21 U.S.C. 352(g)). When space does not permit the "single-dose" term to appear on such products' container labels, then according to 21 CFR 201.10(i)(2), it must appear on the carton or other outer container or wrapper, if space permits, or in the prescribing information. In FDA's experience, there is generally sufficient space to include this information on the carton labeling. Use of the term *single-dose container* does not imply the entire contents of the container constitute a single dose. In some instances, a single-dose container may contain more drug than is required for a single dose. See FDA guidance for industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018).

[79] For additional information on package type terms, please see the Guidance for Industry "Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use."

N. Container Labels for Diluents

When drug products need to be reconstituted or diluted and are copackaged with a diluent that is not clearly labeled, there is a risk for administration of the diluent only. Sponsors should ensure that the word *diluent* is prominently displayed on the PDP to minimize the risk of the diluent being mistaken as the active drug. The following is one example of how this information can be conveyed on the container label:

Diluent
For Drugozide for Injection

Additionally, if room permits, the inclusion of a statement such as *For diluent use only—reconstitute as directed* or *Diluent only – does not contain active drug* on the PDP may also minimize the risk of medication error.

O. Unit Dose Cups for Oral Liquid Drug Products

When oral liquid drug products are packaged in unit dose cups, the strength should be presented as the total quantity per total volume (e.g., 40 mEq per 30 mL in a unit dose cup that contains 30 mL total volume) to ensure that the quantity contained within the unit dose cup is clear to the end user. Confusion can occur when a container label for a unit dose cup does not clearly convey the exact quantity in the container (e.g., a strength may be listed as 20 mEq per 15 mL, but the cup contains 30 mL or 40 mEq).

P. Transdermal and Topical Systems

Transdermal and topical systems should include an identifying label on the backing membrane that includes, at a minimum, the drug name(s) and strength printed with ink that has adequate contrast with the background color and remains visible for the duration of system wear and after disposal to allow for proper identification of the product. The strength of a transdermal system should be expressed as a rate (e.g., XX mg/hour or XX mg/day), whereas the strength of a topical system should be expressed as a percent total drug load (X%). Sponsors are encouraged to incorporate an identifying label early in the product development stage to properly evaluate the impact of the identifying label on the stability of the drug product.[80]

In cases where a transdermal or topical system has heat exposure limitations, a statement similar to *avoid applying heat* may be displayed on the PDP or other panel of the carton labeling, as appropriate, for safety reasons. Additionally, if room permits, the carton labeling can include information on proper disposal of the systems to minimize the risk of accidental exposure and harm to adults, children, and/or pets, including information on when to remove the system for disposal.

[80] See also FDA draft guidance for industry *Transdermal and Topical Delivery Systems - Product Development and Quality Considerations* (November 2019).

Q. Unit Dose Packaging Intended for Hospital Use

When a product is packaged in a container intended for institutional distribution (e.g., unit dose blisters) and the container is not child-resistant, it is recommended that the sponsor include a statement on the carton labeling indicating the package is not child-resistant. For example, the sponsor could include the following on the carton labeling: *This package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be used.* The inclusion of this statement will communicate to health care practitioners that they should dispense the product in an appropriate child-resistant container if the product is to be dispensed for outpatient use.

R. Infusion Containers with Hangers Used for Administration

Sponsors should ensure that hangers attached to infusion containers do not interfere with the ability to read the drug product information on the label. Sponsors should attach a transparent hanger to the container instead of using a portion of the drug label as the hanger.

When an infusion container is hung by its attached hanger during administration, the product information on the container label is displayed upside down. To increase the readability of the container label when the infusion container is hung upside down, sponsors should prominently display the product's proprietary name (if any), established name or proper name, and strength in an inverted manner on the bottom of the PDP or the side panel.

Sponsors should also consider adding graduation marks in milliliters to the infusion container. Having graduation marks on the infusion container can help health care practitioners identify the amount of drug that remains in the infusion container during administration. The graduation marks should be readable when the infusion container is hung upside down for administration.

GLOSSARY

The following terms are described only to assist in understanding how they are used in this guidance, and are not intended for use outside the context of this guidance.

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 container closure system is also known as a packaging system.

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

Dosage Form: As defined in 21 CFR 314.3, the physical manifestation containing the active and inactive ingredients that delivers a dose of the drug product. This includes such factors as:

(1) The physical appearance of the drug product
(2) The physical form of the drug product before it is dispensed to the patient
(3) The way the product is administered
(4) The design features that affect frequency of dosing

Drug Product: A finished dosage form (e.g., tablet, capsule, solution) that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.

Drug Substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient.

End User: Includes, but is not limited to, the patient, patient's caregiver, the physician, the nurse, the pharmacist, the pharmacy technician, and other individuals who are involved in the routine procurement, stocking, storage, selection, dispensing, preparation, and administration of medications (e.g., medication technicians).

Established Name: According to section 502(e)(3) of the FD&C Act (21 U.S.C. 352), with respect to a drug or ingredient thereof, means:

> (A) [T]he applicable official name designated pursuant to section 508 [(21 U.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. [emphasis added]

Fixed-combination drug product: A drug product that contains more than one drug substance.

Label: As defined in section 201(k) of the FD&C Act, "a display of written, printed, or graphic matter upon the immediate container of any article." If any word, statement, or other information is required by the FD&C Act to appear on the label, it must appear on the outside container or wrapper, if there is one, or be "easily legible through the outside container or wrapper."

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

Large-Volume Injections (Large-Volume Parenteral): An injectable dosage form that is packaged in containers labeled as containing more than 100 mL.[81]

Legibility: The ease with which one can distinguish words and letters. Legibility is dependent on the typeface design.

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

Official Drug Product: A drug product for which a monograph is provided.

Package Type: For the purposes of this guidance, a description of the container closure system in which a drug substance or a final drug dosage form is contained.

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

Pharmacy Bulk Package (PBP): The container closure system of a sterile preparation for parenteral use that contains many single doses. The contents are intended for use in a pharmacy admixture program and are restricted to the preparation of admixtures for infusion or, through a sterile transfer device, for the filling of empty sterile syringes. Designation as a PBP is limited to the preparations *injection*, *for injection*, and *injectable emulsion*.

Principal Display Panel (PDP): Refers to the part of a label or labeling that is most likely to be displayed, presented, shown, or examined under customary conditions of display on a pharmacy or retail shelf.

[81] USP General Chapter <659>, Packaging and Storage Requirements.

Prodrugs: Products that are converted to the active moiety after administration.

Proper Name: The nonproprietary name designated by FDA in the license for a biological product licensed under the PHS Act.[82]

Proprietary Name: A drug product's brand name.[83]

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.

Small-Volume Injection (Small-Volume Parenteral): An injectable dosage form that is packaged in a container labeled as containing 100 mL or less.[84]

Tall Man Lettering: A technique that uses uppercase lettering to help differentiate look-alike drug names. Starting on the left side of a drug name, tall man lettering highlights the differences between similar drug names by capitalizing dissimilar letters.[85]

[82] Section 351(a)(1)(B)(i) of the PHS Act (42 U.S.C. 262(a)(1)(B)(i) and § 600.3(k); (21 CFR 600.3(k)).
[83] Sometimes referred to as the product's *trade name*.

[84] USP General Chapter <659>, Packaging and Storage Requirements.

[85] ISMP, "Special Edition: Tall Man Lettering; ISMP Updates Its List of Drug Names with Tall Man Letters," June 2, 2016, https://www.ismp.org/resources/special-edition-tall-man-lettering-ismp-updates-its-list-drug-names-tall-man-letters.