Instructions for Use — Patient Labeling for Human Prescription Drug and Biological Products and Drug-Device and Biologic-Device Combination Products — Content and Format

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Chris Wheeler, 301-796-0151, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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

July 2019
Labeling

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Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
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Instructions for Use — Patient Labeling for Human Prescription Drug and Biological Products and Drug-Device and Biologic-Device Combination Products — Content and Format Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations for developing the content and format of an Instructions for Use (IFU) document for human prescription drug and biological products and drug-device or biologic-device combination products submitted under a new drug application (NDA) or a biologics license application (BLA).[2,3] The IFU is developed by applicants for patients[4] who use drug products that have complicated or detailed patient-use instructions. The recommendations in this guidance are intended to help develop consistent content and format

[1] This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research and the Office of Combination Products at the Food and Drug Administration.

[2] In this guidance, the terms *drug*, *product*, and *product* refer to human prescription drug and biological products that are regulated as drugs, except when there is a difference in the regulation. In such cases, the term *biological products* is used. These terms also refer to drug-device or biologic-device combination products.

[3] For information specific to abbreviated new drug application (ANDA) submissions, please refer to the guidance for industry *Acceptability of Draft Labeling to Support ANDA Approval* (October 2015). 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. An ANDA is required to contain information to show that the labeling proposed for the generic drug is the *same* as the labeling for the reference listed drug (RLD), except for changes required because of differences approved under a suitability petition (see section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR 314.93) or because the generic drug and the RLD are produced or distributed by different manufacturers (see section 505(j)(2)(A)(v) of the FD&C Act).

[4] In this guidance, the terms *patient* and *patients* also refer to caregivers. Some patients are unable to self-administer their drug products because of their age (such as infants and young children) or because of health-related conditions. In such instances, it is important that caregivers be adequately informed on how to safely and effectively administer a drug product to a patient.

across IFUs and to help ensure that patients receive clear, concise information that is easily understood for the safe and effective use of such prescription products.[5] Thus, the recommendations in this guidance are ultimately intended to enhance patients' understanding of IFUs and facilitate the development and approval of IFUs that are clear and helpful to patients.

The recommendations in this guidance do not apply to labeling for standalone medical devices legally marketed under medical device application types[6,7] (i.e., devices that are not constituent parts of drug-device or biologic-device combination products) or to labeling intended for use by health care providers.[8] The recommendations in this guidance also do not apply to devices regulated under a BLA, such as devices associated with blood collection and processing procedures.

This guidance is one of several documents FDA is issuing to fulfill the performance goals under the fifth reauthorization of the prescription drug user fee program, the Prescription Drug User Fee Act (PDUFA) VI. In particular, this guidance relates to the PDUFA VI performance goal regarding guidance on patient-oriented labeling (e.g., instructions-for-use).

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

[5] The IFU is considered part of the product user interface. As such, additional data, such as data from Human Factors (HF) studies, could be utilized to inform the development of the IFU for an NDA or BLA product. The discussion of HF considerations is outside the scope of this guidance. For additional information on development of the user interface and human factors considerations, see the draft guidance for industry and FDA staff *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development* (February 2016). When final, this guidance will represent FDA's current thinking on this topic.

[6] *See* generally sections 510(k), 513(f) and 515 of the FD&C Act.

[7] For information on developing patient labeling for medical devices, including in vitro diagnostic products, please see 21 CFR parts 801 and 809 and the FDA web page at https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/DeviceLabeling/default.htm.

[8] FDA also approves IFUs intended specifically for use by health care providers. These documents include instructions on how to administer a product safely and effectively to patients. However, the recommendations provided in this guidance apply to IFUs intended for use by patients and do not apply to IFUs intended specifically for use by health care providers.

II. BACKGROUND

The IFU is a form of prescription drug labeling for an NDA, BLA, or abbreviated new drug application (ANDA).[9] The IFU is developed by applicants for patients who use drug products that have complicated or detailed patient-use instructions. For example, an IFU may be appropriate for a drug product with one set of dosing instructions for adult patients and another set for pediatric patients. The IFU is developed by the applicant, reviewed and approved by FDA, and provided to patients when the drug product is dispensed.

Applicants should submit true representations of both the content and format of the IFU, including page layout, graphic design, and color, for FDA's review and approval.[10] In general, before implementing and distributing changes to an FDA-approved IFU, applicants should refer to 21 CFR 314.70 or 601.12 for the requirements on submitting changes to previously approved labeling. When the IFU is submitted for FDA review and approval, FDA also requests that the applicant submit the currently approved prescribing information.

III. CONTENT

A. General Content Recommendations

The primary purpose of an IFU is to provide detailed, action-oriented, step-by-step written and visual instructions in a patient-friendly manner. The IFU guides the patient on how to use a prescription drug product and commonly includes instructions on preparation, administration, handling, storage, and disposal. Visuals can complement written instructions and, for some users, can increase comprehension.

1. Consistency With the FDA-Approved Prescribing Information

When reviewing the contents of an IFU, FDA looks for scientific accuracy and consistency with the FDA-approved prescribing information (PI) for the drug product. The IFU must not be false or misleading and must be updated when new information causes the IFU to become inaccurate, false, or misleading.[11]

FDA recommends that the IFU include pertinent information from the PI that describes how to use the drug product. FDA also recommends that the IFU include additional details not typically discussed in the PI where those details are important for the safe and effective use of the drug product by patients (for example, how to administer the drug product using a co-packaged syringe).

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[9] The IFU may be created in addition to a Medication Guide or a patient package insert.

[10] *See* 21 CFR 314.50(e)(2).

[11] *See* section 502(a) of the FD&C Act (21 U.S.C. 352(a)).

The following sections of the PI[12] will generally contain the pertinent information for the IFU:

- DOSAGE AND ADMINISTRATION
- HOW SUPPLIED/STORAGE AND HANDLING
- PATIENT COUNSELING INFORMATION

Information from other sections of the PI may also be useful to include in the IFU.

2. Language and Readability

FDA recommends that the IFU be written in nontechnical language and clearly state the actions a patient should take to use the product. FDA also recommends that the IFU be written in active voice and command language and start sentences or phrases with an action verb when possible. For instance, the IFU can state "Wash your hands" (rather than "You should wash your hands") and "Shake the vial well" (rather than "You should shake the vial well"). FDA suggests writing the IFU in terms that patients are likely to understand, including those with low literacy skills. Overly technical language may deter patients from reading and understanding important information in the IFU.

In general, FDA recommends avoiding abbreviations in the IFU because they may be misinterpreted, which could result in mistakes that may harm a patient. The Agency also recommends writing dose designations (amount and volumetric units) clearly, to avoid medication errors. For instance, FDA suggests avoiding trailing zeros after a decimal point for doses expressed in whole numbers (e.g., state 1 mg rather than 1.0 mg).[13]

3. Headings

Standardized headings in patient labeling materials enhance readability and usefulness (Lorch et al. 2001; Kools et al. 2008; Cowburn and Stockley 2004). Thus, FDA recommends that headings clearly identify the focus of each topic. FDA also generally recommends using subheadings to group related tasks that accomplish a single objective.

Headings and subheadings help organize and differentiate topics so patients can quickly locate information. Section III.B of this guidance provides recommended headings to organize content

[12] The labeling sections noted are pertinent to drug product labeling that must meet the content and format requirements of the final rule "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products," (71 FR 3922, January 24, 2006), available at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. (See also 21 CFR 201.56 and 201.57.)

[13] See also dosage designation information on the List of Error-Prone Abbreviations at the Institute for Safe Medication Practices website (https://www.ismp.org/recommendations/error-prone-abbreviations-list).

in the IFU. The appendix lists the recommended order of all headings described in Section III.B. Additional headings and subheadings can also be useful to include.

FDA recommends tailoring information to each heading such that, in general, specific topics are included under only a single heading.

B. Specific Content Recommendations[14]

FDA recommends that the following information appear in the order listed to ensure consistency and to help patients become familiar with the type and location of information in the IFU.

1. Title

FDA recommends that the title "**INSTRUCTIONS FOR USE**" appear centered prominently at the top of the first page of the IFU, in bold uppercase letters, as follows:

INSTRUCTIONS FOR USE

2. Product Title

FDA recommends that the product title in the IFU include the product's proprietary name,[15] nonproprietary name,[16] dosage form,[17] and route of administration (ROA).[18] The Agency also recommends that the product title appear beginning on the line immediately below the title INSTRUCTIONS FOR USE and that the product title appear centered in bold letters across one, two, or three lines.

For drug products *with* a *proprietary* name, FDA recommends that the information appear in the following order:

Line 1: Proprietary name in uppercase letters, followed by the pronunciation spelling in brackets
Line 2: Nonproprietary name in lowercase letters in parentheses

[14] Text appearing in brackets in the examples indicates a placeholder and should be replaced with the appropriate product-specific information.

[15] In this guidance, *proprietary name* refers to both the proprietary name of a drug product and to the trade name of a biological product. FDA recognizes that not all products have a proprietary name.

[16] In this guidance, the *nonproprietary name* refers to the established name of the drug, if any, or, for biological products licensed under section 351 of the Public Health Service Act, the proper name. (See section 502(e)(3) of the FD&C Act (21 U.S.C. 352(e)(3)); 21 CFR 600.3(k)). For more information related to biological products, see also the guidance for industry *Nonproprietary Naming of Biological Products: Update* (March 2019).

[17] For drug products, the dosage form is part of the nonproprietary name; however, for biological products, the nonproprietary name (proper name) does not include the dosage form.

[18] For some drug products, the route of administration is also part of the nonproprietary name.

Line 3: Dosage form in lowercase letters (if the nonproprietary name does not include the dosage form, such as biological products) followed by the ROA in lowercase letters (if the nonproprietary name does not include the ROA)

Example A: For the fictitious drug product MYDRUG (drugoxide injection), for intramuscular use, FDA recommends that the product title read as follows:

MYDRUG [mye-drug]
(drugoxide injection)
for intramuscular use

Example B: For the fictitious biological product MYBIOLOGIC (replicamab-cznm) injection, for subcutaneous use, FDA recommends that the product title read as follows:

MYBIOLOGIC [my-bye-oh-LAH-jik]
(replicamab-cznm)
injection, for subcutaneous use

For drug products *without* a *proprietary* name, FDA recommends that the product title appear in the following order:

Line 1: Nonproprietary name in title case letters, followed by the pronunciation spelling of the chemical portion of the nonproprietary name in brackets
Line 2: Dosage form in lowercase letters (if the nonproprietary name does not include the dosage form, such as biological products), followed by the ROA in lowercase letters (if the nonproprietary name does not include the ROA)

Example C: For the fictitious drug product Drugoxide Injection, for intramuscular use, which does not have a proprietary name, FDA recommends that the product title read as follows:

Drugoxide Injection [drug-OX-ide]
for intramuscular use

Example D: For the fictitious product Drugoxide Transdermal System, FDA recommends that the product title read as follows:

Drugoxide Transdermal System [drug-OX-ide]

3. Purpose Statement

FDA recommends that the following purpose statement appear below the product title, flush with the left margin:

199 This "Instructions for Use" contains information on how to [insert applicable action
200 verb[19]] [insert Drug Name[20]].
201
202 For example:
203
204 This "Instructions for Use" contains information on how to inject MYDRUG.
205
206 *4. Visual of Drug Product*
207
208 Following the purpose statement, FDA recommends that the IFU display a visual of the drug
209 product and, if applicable (i.e., the drug is a constituent of a combination product), the device(s)
210 used to administer the drug. Choose the best type of visual that clearly depicts the drug product,
211 such as a photograph, simple illustration, or line drawing. If a drug product consists of multiple
212 parts, FDA recommends to visually identify and clearly label each part of the drug product
213 including the device, if applicable. In some cases, it can also be useful to include further
214 explanation of the purpose or function of the parts of the drug product, including the device.
215
216 Generally, FDA recommends that IFUs include a visual of a drug product in an oral dosage form
217 (such as a capsule, tablet, solution, or suspension) where manipulation is necessary to prepare
218 and administer a dose (for example, opening and sprinkling the contents of a capsule). In other
219 instances of drug products in oral dosage forms, patients could likely comprehend the
220 instructions without a visual of the drug product.
221
222 If a drug product is dispensed with multiple components (such as cartridges, blister cards, or
223 packs), FDA recommends that the IFU provide information about all the components and include
224 the following, if applicable:
225
226 - A list of all components dispensed with the drug product
227 - A visual or visuals of the components, clearly identified and labeled
228 - Information explaining the purpose or use of the components
229
230 *5. Important Information for Patients*
231
232 FDA recommends that important information for patients to know before using the drug product
233 be described under the following heading:
234

[19] Insert the appropriate action verb as determined by the product's dosage form; for example, "take" (oral products), "use" (inhalation, ear or eye products), "inject" (injectable products), "apply" (topical or transdermal products), or "insert" (suppositories).

[20] Drug Name is either the proprietary name (if any) or the nonproprietary name of the drug product.

Important Information You Need to Know Before [Insert Applicable Action Verb[21]] [Insert Drug Name]

For example, FDA recommends that the heading for this section of the IFU for the fictitious drug product MYDRUG appear as follows:

Important Information You Need to Know Before Injecting MYDRUG

FDA recommends that the IFU include this heading when patients should take specific actions to prepare, administer, store, or dispose of the drug product to prevent or reduce potentially dangerous consequences that might occur if the specific action is not followed. FDA recommends that information under this heading highlight critical instructions and information to alert patients about the appropriate uses, techniques, and routes of administration that, if not followed, could result in injury.

If confusion could occur about the route of administration based on the dosage form, such as capsules for inhalation that may be mistaken for oral capsules, FDA recommends that the first statement in this section explain how the drug product should be administered. For example:

- **For oral use only** (take by mouth)
- **For subcutaneous injection only** (inject directly into fatty layer under the skin)
- **For topical use only** (apply on top of skin)

Subsequent content that FDA recommends be placed under this heading includes, but is not limited to, the following:

- The timing of a dose relative to a behavior or action specified in labeling; for example:
  - Take [Insert Drug Name] 1 hour before eating.
  - Take [Insert Drug Name] with a meal.
  - Apply [Insert Drug Name] after bathing.
  - Wait at least 2 hours after applying [Insert Drug Name] before showering or swimming.
- Safety information or other important instructions specifically related to administration. For example:

[21] Insert the appropriate action verb ending in "ing" as determined by the product's dosage form; for example, "taking" (oral products), "using" (inhalation, ear or eye products), "injecting" (injectable products), "applying" (topical or transdermal products), or "inserting" (suppositories).

- Swallow tablet whole. Do not cut, crush, or chew tablet.

- Inject [Insert Drug Name] into the thigh. Do not inject [Insert Drug Name] into any other area of the body.

- Instructions to prevent or mitigate the risk of secondary exposure to a drug; for example:

  - To prevent the transfer of [Insert Drug Name] from your body to others, avoid direct skin contact or cover the areas of your body where [Insert Drug Name] has been applied.

6. Preparation Instructions

FDA recommends that instructions on preparing the drug product for use be described under the following heading:

Preparing to [Insert Applicable Action Verb[22]][Insert Drug Name]

For example, FDA recommends that the heading for this section of the IFU for the fictitious drug product MYDRUG appear as follows:

Preparing to Inject MYDRUG

Content that FDA recommends be placed under this heading includes, but is not limited to, the following:

- Information about supplies and materials for administering the dose (for example, a bowl and spoon for mixing a drug product with food; alcohol wipes to prepare an injection; an adhesive bandage to cover an injection site)

- Information about the amount of time required to warm a refrigerated product to room temperature or the maximum amount of time the product may remain unrefrigerated before use

- Instructions to check the drug product for particles or discoloration and to check the expiration date on the product's label

- Directions for assembling parts or components of the product at the time of first use, and if applicable, assembly instructions for subsequent uses

- Instructions for priming topical or inhaled products for first use or priming for subsequent use

[22] See footnote 19.

- Directions for products requiring reconstitution or dilution

- Directions for drawing medication into a syringe

- Instructions on how to insert a co-packaged bottle adaptor

7. Administration Instructions

FDA recommends that instructions for administering the drug product be described under the following heading:

[Insert Applicable Action Verb[23]] [Insert Drug Name]

For example, FDA recommends that the heading for this section of the IFU for the fictitious drug product MYDRUG appear as follows:

Injecting MYDRUG

FDA recommends that information appear as logically ordered, detailed, step-by-step instructions so that patients can safely and effectively take or administer the drug product.

For drug products with more than one method of administration (for example, sprinkle capsule contents into food or drink; administer by feeding tube for patients who have difficulty swallowing), FDA recommends using distinct sections to separate the instructions for each administration method.

Content that FDA recommends be placed under this heading includes, but is not limited to, the following:

- Instructions for preparing the body for administration including, but not limited to, instructions and illustrations specifying which areas of the body are appropriate and inappropriate for potential injection sites

- Instructions for injecting the drug product

- Instructions for rotating the site of application or injection, such as describing the manner of rotation and the importance of keeping track of injection sites to ensure an injection is not given in the same spot for consecutive doses

- Instructions on how to actuate an inhaler to ensure appropriate dosing

[23] Insert the appropriate action verb ending in "ing" concerning administration as determined by the product's dosage form; for example, "taking" (oral products), "using" (inhalation, ear or eye products), "injecting" (injectable products), "applying" (topical or transdermal products), or "inserting" (suppositories).

- Instructions on how to use an auto-injector

- Instructions on how to apply a transdermal patch

8. Storage Instructions

FDA recommends that instructions on appropriate storage be described under the following heading:

Storing [Insert Drug Name]

For example, FDA recommends that the heading for this section for the fictitious drug product MYDRUG appear as follows:

Storing MYDRUG

Content that FDA recommends be placed under this heading includes, but is not limited to, the following:

- Instructions on how to prepare the product for storage (for example, disassembly instructions, washing or cleaning)

- A description of storage conditions (for example, refrigerating the drug product or storing away from light)

9. Disposal Instructions

FDA recommends that disposal instructions be described under the following heading:

Disposing of [Insert Drug Name]

For example, FDA recommends that the heading for this section of the IFU for the fictitious drug product MYDRUG appear as follows:

Disposing of MYDRUG

FDA recommends including this heading when there are specific disposal instructions to prevent the risk of unintended exposure to or harm from products (for example, certain transdermal patches). Under this heading, FDA recommends that the IFU explain how to dispose of the drug product when it is no longer needed, has expired, or is otherwise unusable.

Content that FDA recommends be placed under this heading includes, but is not limited to, the following:

- For items that present a risk of needle stick injury or infection (for example, auto-injectors, pens, syringes), this section should include the appropriate safe sharps disposal language.[24]

- For drug products that require special disposal procedures (for example, outpatient chemotherapeutic drug products), this section should provide specific information for patients on how to appropriately dispose of these drug products.

- For drug products that do not require special disposal procedures, this section should include recommendations for common disposal procedures, such as take-back programs or initiatives, recycling options, or disposal in household trash.

10. Additional Information

At the bottom of the last page of the IFU, FDA recommends that the following information be placed in the order listed below:

(1) Resources for additional information on how to use the drug product, if applicable (for example, a telephone number that patients can call to speak with a customer service representative).

(2) For drug products, include the name and place of business of the manufacturer, packer, or distributor.

(3) For biological products, include the name and place of business of the manufacturer or distributor.

(4) On the last line of the IFU, include the following:

a. The verbatim statement, written as follows:

This "Instructions for Use" has been approved by the U.S. Food and Drug Administration.

b. The verbatim statement is followed by **either** (1) the date of initial FDA approval of the IFU (for example, Approved: January 2019) *or* (2) the date of subsequent FDA approval if the IFU is revised (for example, Revised: May 2019).

[24]Appropriate language to include for safe sharps disposal is available at www.fda.gov/safesharpsdisposal.

IV. FORMAT

Formatting has a large effect on understanding and use of prescription drug information (Koo et al. 2003). The following formatting recommendations are intended to make the IFU easier for patients to read and to help them use prescription drug products safely and effectively (Buck 1998; Koo et al. 2003).

A. Typeface Styling Recommendations

1. Font and Font Size

FDA recommends using a sans-serif font for all text in the IFU, because sans serif is easier to read than a serif type font (American Foundation for the Blind 2017). Recommended sans-serif fonts include, but are not limited to, Verdana and Arial. FDA recommends avoiding the use of any reverse type (such as white or neutral color type on a darker color background), lightface, shading, highlighting, condensed type, or narrow fonts. These techniques can make reading more difficult for patients (Raynor and Dickinson 2009).

Recommendations on font size are intended for easier readability (Buck 1998). Overall, FDA recommends that the font size be no smaller than 10 points (1 point equals 0.0138 inches) for any section of the IFU, except that FDA recommends the following sections appear in font no smaller than 8 points:

- The name and place of business of the manufacturer, packer, or distributor.
- The verbatim statement: This "Instructions for Use" has been approved by the U.S. Food and Drug Administration.
- The date of FDA approval ***or*** revision of the IFU.

2. Letter Case

FDA recommends that the title "**INSTRUCTIONS FOR USE**" appear in all uppercase letters. FDA also recommends that the letter case of the proprietary name or nonproprietary name used in the body of the IFU (excluding the IFU product title) match its appearance in the PI. All other headings in the IFU are recommended to appear in title case. FDA suggests avoiding the use of all uppercase letters in the body of the IFU. The abundant use of uppercased text is difficult to read (Hoffman and Worrall 2004).

3. Bold, Italicized, or Underlined Text

FDA recommends that the following information appear in bold type: **INSTRUCTIONS FOR USE**; **product title,** including **drug name(s), pronunciation spelling**, **dosage form,** and **route of administration**; **headings**; **step numbers**; and **figure titles**. Bolded headings can provide

emphasis that help patients find information quickly and easily (Raynor and Dickinson 2009). However, FDA suggests that bolding, italicizing, and underlining in the body of the IFU be used sparingly and be limited to critical phrases or concepts (for example, important information for patients to know before using the drug product, such as "**For Oral Use Only**"**)**.

B. Page Layout and Design Recommendations

1. Step-by-Step Instructions

FDA recommends that instructions be sequentially numbered, with each step heading appearing in bold type and noted as "**Step 1, Step 2,**" etc. FDA also recommends using continuous numbering throughout the document. For example, FDA suggests avoiding more than one instance of Step 1.

The Agency recommends that action-oriented instruction (for example, "check appearance of liquid following reconstitution") appear before any supporting information particular to performing a step. The Agency also suggests that supporting information appear in bulleted text on a separate line immediately following the corresponding step.

For example:

> **Step 4.** Check the liquid by looking through the viewing window (**Figure F**).
>
> - The liquid should be yellow and should have no lumps or particles.
> - You may see air bubbles. This is normal.

If a patient needs to skip a specific step or set of steps that are not necessary for each dose, FDA recommends that the IFU refer the patient to the next appropriate step. If a patient needs to repeat a step or steps, FDA recommends that the IFU, if appropriate, refer the patient back to the listed step or steps (for example, "Repeat **Steps 10** to **13**, then continue to **Step 14**").

For example:

> **Step 6.** Close your eye for one minute and gently press at the corner of your eye by your nose.
>
> **Step 7.** If you have been instructed by your health care provider to use drops in both eyes, repeat **Steps 3** to **6** in the other eye. If not, skip to **Step 8**.

2. Visuals for Step-by-Step Instructions

Visuals help patients comprehend instructions (Wolf et al. 2010). Thus, FDA recommends that visuals accompany steps classified as critical tasks.[25] Visuals can also be useful for other action tasks and informational text that help a patient understand and safely prepare, administer, store, or dispose the drug product. FDA recommends that visuals be easy to understand, be of adequate size to allow patients to see the focal point, and demonstrate one concept, single idea, or point of information. Photographs can be compelling because they show the most accurate visual representation of a product. However, in some instances, the use of line drawings and sketch illustrations may be most helpful to simplify complexities and highlight key components or avoid distracting details.

FDA recommends that visuals be placed immediately adjacent to the related instructional step. The Agency also recommends that visuals be labeled alphabetically in bold type (such as "**Figure A**, **Figure B,**" etc.). Steps with corresponding figures are recommended to reference the appropriate figure or figures at the end of the step.

For example:

Step 10. Attach the needle to the pen (see **Figure G**).

Figure G

3. Spacing

FDA recommends that the IFU maintain a sufficient balance of text, visuals, and white space. White space can be used carefully to keep the document from appearing cramped, overwhelming, or too spread out (for example, at a minimum, FDA recommends adding a single line before each heading). To aid in reading ease, FDA suggests using white space between blocks of text to separate concepts and to indicate change. Additionally, consider increasing the amount of white space around important text and visuals for emphasis.

4. Color

FDA recommends that the IFU be presented in black type on a white background to facilitate readability. This combination maximizes contrast and legibility and also facilitates uniform reprinting of the document. Colored text and visuals may be useful where all text and visuals maintain clarity and remain legible when the IFU is printed in black and white or in grayscale.

[25] For information on visuals and critical tasks, see the draft guidance for industry and FDA staff *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development*. When final, this guidance will represent FDA's current thinking on this topic.

REFERENCES

American Foundation for the Blind, 2017, Guidelines for Prescription Labeling and Consumer Medication Information for People With Vision Loss, A Collaborative Project of American Society of Consultant Pharmacists Foundation and American Foundation for the Blind, available at http://www.afb.org/info/programs-and-services/public-policy-center/health-and-safety/rx-label-enable-campaign/guidelines-for-prescription-labeling/12345.

Buck ML, 1998, Providing Patients With Written Medication Information, Ann Pharmacother, 32 (9):962–969, https://doi.org/10.1345/aph.17455.

Cowburn, G and L Stockley, 2004, Consumer Understanding and Use of Nutrition Labelling: A Systematic Review, Public Health Nutrition, 8(1): 21–28, https://doi.org/10.1079/PHN2004666.

Hoffmann, T and L Worrall, 2004, Designing Effective Written Health Education Materials: Considerations for Health Professionals, Disabil Rehabil, 26(19):1166–1173, https://dx.doi.org/10.1080/09638280410001724816.

Koo, MM, I Krass, and P Aslani, 2003, Factors Influencing Consumer Use of Written Drug Information, Ann Pharmacother, 37(2):259–267, https://doi.org/10.1177/106002800303700218.

Kools, M, RA Ruiter, MWJ van de Wiel, G Kok, 2008, The Effects of Headings in Information Mapping on Search Speed and Evaluation of a Brief Health Education Text, Journal of Information Science, 34(6):833–844, https://doi.org/10.1177/0165551508089719.

Lorch Jr, RF, EP Lorch, K Ritchey, L McGovern, D Coleman, 2001, Effects of Headings on Text Summarization, Contemporary Educational Psychology, 26(2):171–191, https://doi.org/10.1006/ceps.1999.1037.

Raynor, DK and D Dickinson, 2009, Key Principles to Guide Development of Consumer Medicine Information--Content Analysis of Information Design Texts, Ann Pharmacother, 43(4):700–706, https://doi.org/10.1345/aph.1L522.

Wolf, MS, TC Davis, PF Bass, LM Curtis, LA Lindquist, JA Webb, MV Bocchini, SC Bailey, RM Parker, 2010, Improving Prescription Drug Warnings to Promote Patient Comprehension, Arch Intern Med, 170(1):50–56, doi: 10.1001/archinternmed.2009.454.

APPENDIX — INSTRUCTIONS FOR USE: RECOMMENDED ORDER OF INFORMATION

Numbers in parentheses correspond to items 1 through 10 in Section III.B, Specific Content Recommendations. The main body of this guidance contains detailed information about each item. The example used is for a drug product.

(1) **INSTRUCTIONS FOR USE**
(2) **[Insert Product Title]**

(3) This "Instructions for Use" contains information on how to [insert applicable action verb[1]] [**Insert Drug Name**[2]]

(4) [Insert visual of drug product]

(5) **Important Information You Need to Know Before [Insert Applicable Action Verb[3]] [Insert Drug Name]**

(6) **Preparing to [Insert Applicable Action Verb[4]] [Insert Drug Name]**

(7) **[Insert Applicable Action Verb[5]] [Insert Drug Name]**

(8) **Storing [Insert Drug Name]**

(9) **Disposing of [Insert Drug Name]**

(10) [Insert resources for additional information on how to use the drug product (for example, a telephone number that patients can call to speak with a customer service representative)]

(10) [Insert name and place of business of manufacturer, packer, or distributor of drug product]

(10) This "Instructions for Use" has been approved by the U.S. Food and Drug Administration. Approved: [insert Month Year]
or
Revised: [insert Month Year]

[1] Insert the appropriate action verb as determined by the product's dosage form; for example, "take" (oral products), "use" (inhalation, ear or eye products), "inject" (injectable products), "apply" (topical or transdermal products), or "insert" (suppositories).

[2] Drug Name is either the proprietary name (if any) or the nonproprietary name of the drug product.

[3] Insert the appropriate action verb ending in "ing" as determined by the product's dosage form; for example, "taking" (oral products), "using" (inhalation, ear or eye products), "injecting" (injectable products), "applying" (topical or transdermal products), or "inserting" (suppositories).

[4] See footnote 1.

[5] Insert the appropriate action verb ending in "ing" concerning administration as determined by the product's dosage form; for example, "taking" (oral products), "using" (inhalation, ear or eye products), "injecting" (injectable products), "applying" (topical or transdermal products), or "inserting" (suppositories).