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FDA Finalizes 'Instructions for Use' Guidance on Patient Labeling for Drugs and Biologics

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As companies begin planning for the upcoming year, attorneys who sit on promotional review committees should consider the significant guidance published by the U.S. Food and Drug Administration ("FDA") and update process aids and related trainings. For example, this summer, FDA finalized its guidance for developing both the content and format of patient Instructions for Use ("IFU") inserts for prescription drugs and biological products, and drug-led or biologic-led combination products submitted under a new drug application ("NDA") or biologics license application ("BLA") (the "Guidance").[1] IFUs are written for patients or caregivers who use drug products that have complicated or detailed patient use instructions (to promote the safe and effective use of the drug).[2] The IFU is developed by the applicant (i.e., the manufacturer), reviewed and approved by FDA, and provided to patients when the product is dispensed.

The final Guidance clarifies a number of important points, including advice on meeting with FDA to discuss the IFU during the investigational new drug ("IND") phase and expanding the content of the Guidance from drug-device combination to drug-led combination products.[3]

Key Takeaways of the Guidance

This Guidance is one of several documents being issued by the Agency to fulfill its performance goals under the fifth authorization of the Prescription Drug User Fee Act ("PDUFA") VI. The recommendations are intended to inform the development of patient IFUs so that they are clear, concise, and easily understood to further ensure the safe and effective use of covered products.

IFU Content

The Guidance breaks down content recommendations into two categories—general content recommendations and specific content recommendations.

Under its general content recommendations, FDA recognizes that although IFUs must be consistent with the approved Prescribing Information ("PI"), the IFUs can and typically do include additional information that is necessary for the user. IFUs should also be using language to facilitate understanding and readability by patients with low literacy skill, including headings and subheadings that clearly identify the focus of each topic in the IFU.

The Guidance also offers ten specific content recommendations addressing all aspects of IFUs, including:

1. Displaying the ***Title*** of the document
    a. "INSTRUCTIONS FOR USE" should appear centered prominently at the top of the first page of the IFU in bold, uppercase letters.
2. Displaying the ***Product Title***
    a. The IFU should include the product's proprietary name, non-proprietary name, dosage form, route of administration, and controlled substance schedule when applicable.
3. Displaying the ***Purpose Statement***
    a. FDA advises that the statement "This Instructions for Use contains information on how to [insert applicable action verb] [insert Drug Name]" appear in the IFU.
4. Displaying a ***Visual of the Drug Product***
    a. FDA suggests that the IFU contain an image of the product, and, if part of a combination product, the associated device. Manufacturers should "[c]hoose the best type of visual that clearly depicts the drug product, such as a photograph, simple illustration, or line drawing."
5. ***Important Information for Patients***
    a. FDA recommends describing any important patient information under the heading "Important Information You Need to Know Before [Insert Applicable Action Verb] [Insert Drug Name]" (e.g., when patients should take specific actions to prepare, administer, store, and/or dispose of the drug product to prevent or reduce potentially serious outcomes).
6. ***Preparation Instructions***
    a. FDA advises describing product preparation instructions under the heading "Preparing to [Insert Applicable Action Verb] [Insert Drug Name]," and provides specific examples of what content should be included in this part of the IFU.
7. ***Administration Instructions***
    a. FDA suggests describing instructions for administering the drug product under the heading "[Insert Applicable Action Verb] [Insert Drug Name]" and clearly stating the sequence of actions required to administer the drug.
8. ***Storage Instructions***
    a. FDA recommends placing any instructions related to product storage under the heading "Storing [Insert Drug Name]" with instructions on how to prepare the product for storage, a description of storage conditions, or a "keep out of reach of children" statement.

9. ***Disposal Instructions***

    a. FDA recommends that any disposal instructions follow the heading "Disposing of [Insert Drug Name]" and include safe disposal instructions for items that present a risk of a needle stick injury, as well as specific information on how to appropriately dispose of drug products.

10. ***Additional Information***

    a. FDA advises that any additional information follow a certain order:

        1. resources for additional information;

        2. the name and place of business of the manufacturer, packer, and/or distributor for products marketed under a new drug application;

        3. the name, address, and license number of the manufacturer for products marketed under a BLA;

        4. the verbatim statement "This Instructions for Use has been approved by the U.S. Food and Drug Administration" followed by the month and year of initial IFU approval by FDA or the month and year of the subsequent revision to the IFU.

IFU Format

The Guidance also provides recommendations related to IFU format intended to make the IFU easier for patients to read. These formatting recommendations include:

1. ***Typeface styling recommendations such*** as:

    a. Using sans-serif font and a font size no smaller than 10 points;

    b. Utilizing uppercase letters for "INSTRUCTIONS FOR USE;" and

    c. Reserving bold text for the product title and other important phrases or concepts.

2. ***Page layout and design recommendations*** such as:

    a. Providing instructions sequentially numbered with each step heading appearing in bold type;

    b. Offering visuals for the step-by-step instructions;

    c. Using spacing and white space to separate concepts and indicate change; and

    d. Presenting the IFU in black type on a white background for ease of readability.

Differences Between the Final Guidance and the Draft Guidance

This final Guidance makes minor changes to the draft version released for comment in July 2019. Most of the changes are editorial and intended to provide additional clarity. These changes include:

- **Including discussion of the role of human factors in informing the development of an IFU** (see footnote 6 in the Guidance). The final Guidance clarifies that the IFU is considered part of the "product user interface" and the need for an IFU may be informed by following the human factors engineering process, including conducting use-related risk analyses ("URRA") to determine whether an IFU is necessary. Accordingly, the Guidance suggests that inclusion of an IFU document can be implemented as a mitigation for use-related risk.
- **New language on labeling for drugs of self-administration.**[4]
- **New language in the "additional information" section.** The final Guidance suggests that labeling should include a phone number for reporting problems with products and/or reporting adverse events.
- **New language advising applicants to meet with FDA to discuss the IFU during the IND phase.**[5]
- **Modification to the title and scope of the Guidance from drug-device combination to drug-led combination products.** The Guidance states that its recommendations do not apply to stand-alone devices or device constituent parts of cross-labeled combination products if the device constituent is marketed under a device authorization, or stand-alone devices regulated under a BLA (e.g., those associated with blood collection).[6]

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[1] Instructions for Use – Patient Labeling for Human Prescription Drug and Biological Products – Content and Format, Guidance for Industry, Food and Drug Admin. (July 2022).

[2] The recommendations in the Guidance do not apply to labeling for stand-alone devices or for device constituent parts of cross-labeled combination products if the device constituent is marketed under a device authorization (i.e., devices that are not constituent parts of drug-device, biologic-device, or biologic-drug-device combination products submitted under BLA or NDA), labeling for combination products for which the device constituent part provides the primary mode of action, or labeling intended for use by health care providers. The recommendations in this Guidance also do not apply to stand-alone devices regulated under a BLA, such as devices associated with blood collection and processing procedures.

[3] Applicants must submit true representations of both the content and format of the IFU for FDA's review and approval and, according to the Guidance, applicants are encouraged to "meet with FDA as early as the investigational new drug application (IND)/pre-IND phase, if appropriate, to discuss the development of any IFU."

[4] Page 3. "For drugs for which self-administration may be complicated (such as requiring the patient to perform multiple steps to prepare, administer, store, and/or dispose the drug), the IFU is intended to give directions that are clear and understandable for patients, and therefore, promote the safe and effective use of that drug."

[5] Page 3. "The Agency encourages applicants to meet with FDA as early as the investigational new drug application (IND)/pre-IND phase, if appropriate, to discuss the development of any IFU."

[6] Page 2.