Combination Products Coalition

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VIA ELECTRONIC SUBMISSION

August 28, 2019

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2019-D-1615: Instructions for Use—Patient Labeling for Human Prescription Drug and Biological Products and Drug-Device and Biologic-Device Combination Products—Content and Format: Draft Guidance for Industry

Dear Sir or Madam:

The Combination Products Coalition ("CPC")[1] welcomes the opportunity to offer comments on FDA's "Instructions for Use—Patient Labeling for Human Prescription Drug and Biological Products and Drug-Device and Biologic-Device Combination Products—Content and Format: Draft Guidance for Industry" (hereinafter the "Draft Guidance").

While the CPC appreciates the value of this Draft Guidance in providing FDA's expectations for Instructions for Use ("IFU") to ensure a more consistent review experience, especially for combination products, the CPC has some concerns and suggestions for improvement as detailed below. We hope that as FDA finalizes its guidance, it will consider our comments as the cumulative voice of learnings from subject matter experts who have written, designed, and tested hundreds of IFUs for combination products. We further hope these learnings will be leveraged to provide a flexible yet consistent guidance (rather than requirements) for IFUs that optimize user experiences while protecting user safety.

Although the CPC agrees with many of the suggestions in the Draft Guidance, we recommend that FDA revise the document to:

1. Clarify that the final layout and content of an IFU should be based on outcomes of the human factors ("HF") process and the expertise of instructional design professionals, and that the content and layout proposed within the Draft Guidance are suggested, but not required;

2. Provide clearer guidance on the criteria by which a manufacturer decides whether a product requires an IFU;

[1] The CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in combination product issues. One of our top priorities is to work collaboratively with FDA on issues affecting combination products to advance our common mission: providing the best possible health care to patients. Our diverse, cross-industry membership permits the CPC to bring a special, broad and unique perspective to these issues.

3. Clarify the scope of the Draft Guidance; and

4. Provide additional guidance on how and when IFUs are to be submitted for review.

Below, we present our major observations and concerns surrounding the four proposed areas for revision listed above. We have also included additional, specific comments in Appendix A.

I. Final Layout and Content Based on HF Considerations and Instructional Design Expertise

A. HF Considerations

Rather than excluding HF considerations from the scope of the Draft Guidance (as noted in footnote 5), the CPC believes that the Draft Guidance should allow for supportive HF data to support IFU content or design that may vary or depart from the recommendations made in the Draft Guidance. In practice, FDA has expected the IFU to be developed and tested alongside the rest of the product user interface using a HF process, in accordance with FDA HF guidance documents.[2] Therefore, implying that IFUs will be accepted by FDA by simply ensuring the IFU is aligned with the USPI and following the formatting detailed in the Draft Guidance could be misleading and may confuse applicants due to contradictions with existing FDA HF guidance documents. While there are some advantages in standardizing the content and layout of instructional content, products must still meet the needs of their distinct user population(s), use environments, and use scenarios. As a result, testing an IFU developed with the recommendations made in the Draft Guidance may potentially result in use issues during HF studies. Changing an IFU to meet guidance recommendations, either immediately before a HF Validation study is conducted or after the study is complete, may invalidate the development work that has already been done to optimize the IFU for the product's particular user group. To that end, we propose adding the following text and footnote to the Draft Guidance after line 72:

> **Text:** "The IFU is designed and developed based on an iterative process using use-related risk assessments, HF principles, and usability studies, in accordance with previous FDA HF Guidance Documents.* The IFU should be revised accordingly based on HF study findings."
>
> **Footnote:** **Applying Human Factors and Usability Engineering to Medical Devices: Guidance for Industry and FDA Staff* (Feb. 2016) & *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development: Draft Guidance for Industry and FDA Staff* (Feb. 2016).

B. Leveraging Instructional Design Expertise

Applicants may have access to instructional design professionals who, through applying a rigorous HF process, can bring significant design intelligence to IFU development and superior graphical techniques and mechanisms that make IFUs easier to read and comprehend, and more acceptable to users. The Draft Guidance is most likely to be viewed as FDA's "preferred" approach (as inferred by the statement on lines 7-8: "This draft guidance, when finalized, will represent the current thinking of [FDA] on this topic"), and therefore considered a requirement by IFU developers. However, if developers strictly adhere to the Draft Guidance, opportunities to advance readability, comprehensibility and acceptability (all within the skill set

[2] *E.g.*, FDA, *Applying Human Factors and Usability Engineering to Medical Devices: Guidance for Industry and FDA Staff* (Feb. 2016) & FDA, *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development: Draft Guidance for Industry and FDA Staff* (Feb. 2016).

and capability of experienced design professionals) may be missed. Allowance needs to be made in the Draft Guidance for other well-established and innovative document and graphical design mechanisms to improve the outcomes of user interaction with IFUs. Also, for a previously reviewed and approved IFU for a highly similar product within an applicant's product portfolio, preference should be made for IFU content and layout that aligns with the other products (assuming that the user groups and abilities are similar). In addition, to leverage FDA's experience reviewing the HF study results of many products and their IFUs, the Draft Guidance should consider highlighting any content or layout options that are *not* recommended (and provide reasons why).

C. Suggestions vs. Requirements

The content section of the Draft Guidance proposes a cluster of design solutions that may be unnecessarily constraining. Much greater flexibility could be achieved—and potentially more appropriate solutions—if the functional requirement for each element was presented, leaving the applicant to develop the design solutions, and demonstrate through appropriate HF processes that the IFU design leads to safe and effective use of the medicinal product by the intended user population. To reduce regulatory compliance risks, manufacturers may feel compelled to adhere rigidly to the Draft Guidance, rather than explore alternative design approaches that may be more effective at "enhanc[ing] patients' understanding" (line 25) than the solutions proposed in the Draft Guidance. Some examples of design solutions that may be unnecessarily constraining, and where we would recommend revision, include:

- **Lines 136-139, 152-153, 477-478, recommendation for all uppercase letters**: The recommendation to use all uppercase letters for the proprietary name for an IFU conflicts with guidance on Proprietary, Established, and Proper Names in FDA's *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors: Draft Guidance for Industry* (April 2013), which recommends "capitalizing only the first letter in the proprietary name because words written in all-capital letters are less legible than words written in mixed case letters." As IFUs are considered patient labeling similar to container labels and carton labeling, the information in these two guidance documents are conflicting. As an alternative, recommendations on the functional requirement for the title could be specified, for instance: "The title 'Instructions for Use' must appear clearly and prominently at the start of the IFU." Alternatively, adding "if space allows" would increase flexibility if limited space on the IFU cover precludes the use of all-caps (which tend to take up more space than initial capitalization).

- **Lines 146-147, product title centered in bold letters across one, two, or three lines:** A more flexible solution would be to specify the purpose and requirements of the specific element, for instance: "'The product's proprietary name, nonproprietary name, dosage form, and route of administration (ROA) should appear clearly and prominently at the start of the IFU, and be visually associated - either by proximity or through graphical devices - with the title 'Instructions for Use.'"

- **Lines 155-163, 173-191, phonetic spellings**: Offering a phonetic spelling without an explanation assumes that readers know what they are and how to use them. The unfamiliar phonetic spelling will appear in close proximity to other complicated or unfamiliar names and may not improve clarity in an already potentially confusing block of unfamiliar text at the start of the IFU. If offering the phonetic spelling helps users, for example, those who may need to verbally refer to the product name, consider preceding it with an explanation, such as: "Mydrug [if spoken, say "Mye-drug"]."

- **Lines 196-197, purpose statement:** This statement on the cover could compete for space, particularly for combination products where the image of the device component may need to be maximized. Much greater flexibility could be achieved if the functional requirement for the purpose

statement was specified, for instance, "A clear, concise statement of purpose of the IFU should lead the introductory text."

- **Line 499, "Step 1, Step 2":** To reduce visual complexity, we believe that numbering steps, without necessarily prefacing each number with the word "Step," should be sufficient. Using the word "Step" may be more useful for meta headings, but may create too much visual noise and impact readability of step sub-headings.

II. Criteria By Which a Manufacturer Decides Whether a Product Requires an IFU

A. Drug-only Product vs. Combination Product vs. Device Component of Combination Product

The CPC recommends either deleting the terms "complicated" and "detailed" in lines 21 and 51 or adding specific criteria by which developers can decide whether or not an IFU might be required for a product. The terms "complicated," "detailed," or "where manipulation is necessary" (line 217) are highly subjective and ambiguous terms. Products with simple tasks also need good instructions and a product-naïve user could find the IFU to be complicated. The CPC recommends that the decision whether to create an IFU should be based on the outcome of the use-related risk analysis, conducted per expectations described in other FDA guidance documents.[3] The outcome of the risk analysis informs the need for additional controls in the form of user interface design, including: product labeling, device design (if applicable), packaging, an IFU (if applicable), the Prescribing Information, Medication Guide, and any other instructional materials. By distinguishing "Human Prescription Drug and Biological Products" from "Drug-Device and Biologic-Device Combination Products" in the title of the document, we assume the scope of this Draft Guidance includes non-combination products. However, we ask that FDA clarify whether all non-combination products are automatically expected to have an IFU, or whether a risk analysis can be conducted to determine whether an IFU is an appropriate or effective control (the latter being the preferred approach). We also ask for clarification on FDA's recommendation on line 532 to classify steps as "critical tasks" and whether this means that use-related risk analyses (the tool for determining critical tasks) will be expected for all non-combination products.

Further, the term "drug product" throughout the document should be clarified as it could be interpreted to mean only the drug constituent part of a combination product and not the biologic or device constituent part of combination products. This term should be explained to clarify which aspects of the Draft Guidance are applicable to drug, device, and biologic constituent parts, as well as the combination product as a whole.

B. New vs. Changing IFUs

The CPC requests that the Agency clarify how the Draft Guidance is applicable to newly-developed IFUs and changes being made to existing FDA-approved IFUs, acknowledging that already approved IFUs would not need to be revised to align with the recommendations provided in the Draft Guidance. An announcement of an implementation schedule or transition period following the publication of the final version of this guidance would be appreciated. Moreover, we ask that FDA clarify the types of post approval supplements that would be expected for minor clarifications to an IFU step. The relevant regulation, 21

[3] *E.g.*, FDA, *Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications: Draft Guidance for Industry and FDA Staff* (Sept. 2018) & FDA, *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development: Draft Guidance for Industry and FDA Staff* (Feb. 2016).

CFR 314.70, poorly addresses the kinds of supplements that may be required for IFU changes. For example, very minor textual or figure changes can require a six-month labeling change supplement which can delay changes that could benefit certain users. In contrast, minor IFU changes to update figures or IFU descriptions (such as when minor changes to a device component warrant changes to words or figures) or other text following a minor device constituent part change may follow the timeline for a four-month manufacturing supplement, CBE, CBE 30,foo or Annual Report. We also request acknowledgement in the Draft Guidance that if an applicant can demonstrate that the IFU of the device constituent's legal manufacturer is sufficient, no additional IFU for the combination product would be required.

III. Clarifying the Scope of the Draft Guidance

The scope of the Draft Guidance is currently for patients (line 21) and caregivers (footnote 4) and excludes health care providers ("HCPs") (footnote 8). The CPC requests acknowledgement in the Draft Guidance that, although the target audience is lay-users (i.e., patients and caregivers), HCPs may also use an IFU, for example, when using a product for the first time or explaining to a lay-user how to use the product.

As discussed in Section I above, applicants should be able to develop, with sufficient flexibility, IFUs suitable for the intended users (be they medically trained or not) based on their determination of whether intended users would or would not be familiar with or have experience with the new product. The use-related risk analysis should be used to determine the appropriate level of control that can be realized by the product's IFU. Thus, we recommend replacing "patients" with "users" on lines 104 and 132.

IV. Guidance on How and When IFUs Are to be Submitted for Review

The CPC requests that FDA provide clarification around timing for submission and review of IFUs. The recommendation in Section III.A.1. of the Draft Guidance that the IFU be consistent with "FDA-Approved" Prescribing Information is confusing because it implies that the PI would be approved *before* the IFU is reviewed, which may not be true for all products. Particularly for combination products, per the FDA draft guidance *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development*, FDA expects "Intend-to-market labels and labeling (including instructions for use if any are proposed)"[4] to be submitted *with* the HF Validation study protocol. In that case, the IFU would be reviewed and validated *before* NDA or BLA submission, and before PI review.

The CPC would like the Draft Guidance to remind applicants to seek early Agency feedback on the content and format of the IFU especially if there is expectation for validation in a HF study. Early feedback will help ensure that any comments or proposed revisions can be incorporated in the IFU and evaluated prior to execution of the HF Validation study. Applicants will be more readily able to accept proposed changes to the IFU pre-validation as opposed to during review as part of a marketing submission where there may be a negative impact of the proposed changes on the validated IFU. For example, if the layout is altered significantly it may be difficult for patients to find relevant information. To align with existing FDA draft guidance documents,[5] which encourage submission of the IFU as part of the HF Validation study protocol submission, the CPC requests inclusion of the following statement in the Draft Guidance, "For

[4] FDA, *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development: Draft Guidance for Industry and FDA Staff* at 15 (line 546) (Feb. 2016).

[5] *E.g.*, FDA, *Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications: Draft Guidance for Industry and FDA Staff* (Sept. 2018) & FDA, *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development: Draft Guidance for Industry and FDA Staff* (Feb. 2016).

combination products (containing a device constituent part) FDA encourages applicants to submit the instructions for use (IFU) as part of the HF Validation study Protocol submission for Agency review prior to execution of the HF Validation study. Feedback on the IFU content and format will be provided by the Agency as part of this HF Validation study Protocol submission review." Further, to acknowledge the recommendations for IFU content and formatting included in existing FDA draft guidance documents, the CPC requests inclusion of the following statement after line 27: "The recommendations in this guidance supplement recommendations on IFU development that are contained in other relevant FDA guidance documents." We also request that this statement include a footnote that lists relevant references, such as FDA's *Metered Dose Inhaler (MDI) and Dry Powder Inhaler 5(DPI) Products - Quality Considerations* (April 2018).

If an IFU is not submitted as part of the HF Validation study protocol, the Draft Guidance should clarify how IFU content is to be submitted: physically or digitally, number of samples, whether a Word version is expected in addition to the intended commercial printed layout version (similar to the text in FDA's draft guidance *Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications* (lines 166-169)), and in which module the content and layout are expected (e.g., Module 1 of the eCTD). While we are not aware of any regulation or guidance document requiring both the content (Word document) as well as the layout (artwork PDF) to be submitted to FDA, in practice, FDA has consistently asked that both be submitted in Module 1. Overall, we ask that references in the Draft Guidance be aligned with other related FDA guidance documents containing recommendations for IFU submission to ensure manufacturers apply an approach consistent with all FDA guidance documents.

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We appreciate the opportunity to provide input on the Draft Guidance and are happy to meet with the Agency to clarify or discuss any of our suggestions.

Yours truly,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition

Appendix A: Additional Requested Revisions

Line Reference	Draft Guidance Text	Proposed Revision/Comment	Rationale
Footnote 4	Some patients are unable to self-administer their drug products…	After "unable," insert "or do not want…"	Some patients are able, but do not want to self-administer medication.
56	Applicants should submit true representations of both the content and format of the IFU…	Clarify "true" or replace with "accurate." Also, clarify in the Draft Guidance when the applicant should submit the "true" (or accurate) representation (e.g., at the time of submission or after labeling negotiations). If representation is expected at initial submission, the Draft Guidance should clarify whether subsequent iterations will need to follow the same format or can be in the form of a manuscript with black and white figures.	Context and meaning of the word "true" in this sentence is unclear. If the intention is to indicate the accuracy of the IFU, then suggest use of/replacement with the term "accurate" as proposed.
60-61	When the IFU is submitted for FDA review and approval, FDA also requests that the applicant submit the currently approved prescribing information.	Revise to read: …FDA also requests that the applicant submit the currently approved or anticipated prescribing information with the initial IFU and in subsequent changes until final approval is reached.	Revision allows flexibility for the situation in which an IFU is submitted for a new product (for which the PI is not yet approved) or for a product for which the PI has already been approved. Please note that there are situations where the drug and device are in development at the same time in which it is impossible to provide even the "anticipated" prescribing information.
68	The primary purpose of an IFU is to provide detailed…	Change "detailed" to "sufficiently detailed."	Full detail may not be necessary and may decrease comprehension or deter users from reading the IFU if it makes the IFU more verbose.
71-72	Visuals can complement written instructions and, for some users, can increase comprehension.	The Draft Guidance should emphasize improving the effectiveness of the visuals and allow applicants to demonstrate through HF testing that visually-led instructions (rather than text alone) could ensure safe and effective use.	This statement downplays the power and effectiveness of well-considered and executed visuals, which can reduce text burden and make instructions seem less onerous to the reader, and potentially much more likely to be read in full.

Line Reference	Draft Guidance Text	Proposed Revision/Comment	Rationale
76-77	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.	Add highlighted: …with the FDA-approved or anticipated prescribing information…	Revision accommodates both the initial IFU and subsequent changes to an approved IFU.
76-77	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.	Clarify that this statement may not apply for products not yet marketed (and for which a final PI may not be available at the time the IFU is created).	Clarification needed because statement assumes a PI already exists and that IFU is being drafted and/or changed. At the time of IFU review, the applicant may not have an approved PI.
77-79	The IFU must not be false or misleading…	Change highlighted to: The IFU must not be inaccurate…	IFUs are designed with the best intention to support the users/patients in safely and effectively administering the treatment; the term "inaccurate" is sufficient.
81-85	FDA recommends that the IFU include pertinent information from the PI...	Draft Guidance should recommend that the PI reference the IFU, if an IFU exists.	The PI may still the primary source of information but if an IFU is required, this should be communicated in the PI also.
81-85	FDA recommends that the IFU include pertinent information from the PI...	More clarity is requested with regard to where and how to incorporate the PI, specifically what information is considered "pertinent."	Rationale included within proposed change.
82-85	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…	Suggest that the Draft Guidance require the "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" be included in other sections of the PI, e.g., Section 17 – Patient Counseling information.	More information in the IFU than that in the PI may cause confusion among HCPs or patients.
95	Information from other sections of the PI may also be useful to include in the IFU.	Add after line 95, "…but duplication should be avoided apart from essential information."	Examples of what should be included would be useful to prevent adding extraneous information which may distract from the core purpose of the IFU.
102-103	For instance, the IFU can state… "Shake the vial well" (rather than "You should shake the vial well").	Propose modifying text of this example to be more descriptive and to help comprehension, e.g., replace "well" to "…until the liquid is clear and all particles are dissolved."	Instructions should clarify information and using an example that does not align with HF principles could encourage poorly written instructions.

Line Reference	Draft Guidance Text	Proposed Revision/Comment	Rationale
103-104	FDA suggests writing the IFU in terms that patients are likely to understand, including those with low literacy skills.	Clarify "low literacy skills," perhaps by specifying the grade level of literacy that the IFU should be written in accordance with and referencing existing CDRH Guidance on Medical Device Patient Labeling.	Alignment with existing Agency guidance documents.
108-112	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).	(1) Replace "patient" with "patient, user or someone who comes into contact with the product." (2) Add an example for avoiding abbreviations (e.g., use "pre-filled syringe" instead "PFS") and start a new paragraph for the dose designations. (3) Add at the end of the last sentence, "…except in the instances where distinction is necessary, for instance, if the instruction refers to both a 1.2 mg dose and a 1.0 mg dose."	Suggested revisions provide additional clarity.
118-122	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.	Add a note that graphical devices can also aid navigation by reducing an overwhelming amount of text required to be read.	Rationale included within proposed change.
131-132	FDA recommends that the following information appear in the order listed...	Allow some flexibility in the order of preparation, administration, storage, and disposal instructions depending on the product task analysis.	The content organization proposed here may not be appropriate for both single-use and multi-use products. As determined by the HF process, an alternative ordering scheme may be appropriate to enhance usability.
132	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.	Remove or clarify expectation of "familiarity."	Infrequent users are less likely to benefit from an increase in familiarity, and regular or multiple medicinal product users could be fatigued or confused by apparently similar formats between different products. Given that medicinal products differ so widely in complexity, form, administration process,

Line Reference	Draft Guidance Text	Proposed Revision/Comment	Rationale
			potency, risk, and many other factors, burdening all products with the same construct seems unnecessary, and potentially adds risk for patients on multiple medications.
143-144	FDA recommends that the product title in the IFU include the product's proprietary name, nonproprietary name, dosage form, and route of administration (ROA).	Add after this sentence: "In cases where there are multiple products under the same nonproprietary name, dosage form and ROA, the appropriate device type should also be listed to aid in differentiation."	The device may be the largest differentiator between multiple products with similar dosage and ROA. Including the device in the product title would also further differentiate between products.
143-144	FDA recommends that the product title in the IFU…	It would be helpful to include an example of a fictitious drug that is scheduled.	For a drug that is scheduled, the product title needs to reflect the scheduling information.
159-172	Examples A and B for MYDRUG and MYBIOLOGIC	The Draft Guidance should explain FDA's preference for use of trademark and registered trademark symbols. For example, FDA typically permits these symbols only once whereas many proposed IFUs submitted for approval may use them on each use of the tradename.	This advice would save unnecessary discussion and review edits in the development and approval of the IFU.
199-200	This "Instructions for Use" contains information on how to [insert applicable action verb] [insert Drug Name].	Change to: "Instructions for Use" contains information on how to [insert applicable action verb] [insert Drug Name]. [For chronic drug indications] Read these Instructions for Use before you start using [insert Drug Name] and each time you get a refill. There may be new information.	Reiterates that these instructions are intended to be read each time the product is used and also covers instances where reusable products have been refilled as there may be specific instructions around this process.
206	*4. Visual of Drug Product*	Suggest revising to "*Visual of Drug Product and/or Device User Interface*." This section could be located after Section 5 as it would describe the product immediately before use steps are read by the user.	Clarifies assumed intent of this statement to show the overall product user interface (including device if applicable) rather than just the drug product.
212-213	…clearly label each part of the drug product including the device, if applicable.	Clarify that labeling is only required if reference is made to each part in the rest of the IFU.	Rationale included within proposed change.

Line Reference	Draft Guidance Text	Proposed Revision/Comment	Rationale
216-218	Generally, FDA recommends that IFUs include a visual of a drug product…where manipulation is necessary to prepare and administer a dose…	Clarify that a visual of the manipulation itself should be embedded within the textual instructions.	Presenting visuals of product manipulation before textual instructions may cause a user to prematurely administer the drug without consulting the remainder of the instructional materials. Placing this visual within the context of the textual instructions is more likely to influence correct performance.
228	• Information explaining the purpose or use of the components	Clarify recommended location for this information.	If only included with the visual, users may not read the rest of the stepwise instructions and miss key instructional information to safely and effectively use the product.
230	*5. Important Information for Patients*	Clarify what type of information is considered "Important."	This heading infers that the rest of the IFU is less important and may encourage users to skim the remainder of the document.
235	**Important Information You Need to Know Before…**	Trim this heading to "Important Information."	IFU panels tend to be narrow and these words would run to multiple lines which would compromise readability. This suggestion may work better on a large sheet format (such as an unfolded PI sheet), but is ill-suited to typical accordion fold formats where it is desirable not to have images and type extend across fold lines.
243-245	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.	Replace highlighted text to: FDA recommends that the IFU include this heading when patients should be aware of specific important information ***prior*** to preparing, administering, storing, or disposing of the drug product to prevent or reduce potentially dangerous consequences that might occur if the specific action is not followed.	Clarifies that the section provides important information before administration rather than being an instruction related to a specific step. Including instructions out of context related to critical tasks may confuse users who may see instructional steps and begin administration without consulting the remainder of the instructions.
246, 248	…highlight critical instructions…that, if not followed, could result in injury.	Clarify in the Draft Guidance, perhaps by way of a footnote to other draft guidance documents, whether "critical instructions" are considered to be "critical tasks."	Ensures terminology aligns with other guidance documents and helps applicants understand FDA's expectations of how to categorize use steps.

Line Reference	Draft Guidance Text	Proposed Revision/Comment	Rationale
254-262	• **For oral use only…**	Also include statements about certain delivery devices that would require HCP training for patient use (especially for self-administration at home) and for first use.	Would substantially reduce the risk of medication errors; FDA has allowed this type of statement on multiple occasions for multiple products.
254-257	• **For oral use only…**	Recommend using lay-person's language and delete the technical version.	Unless technical terms must be explained (for example, they appear in the product title), information that is too technical would not be understood.
260-271	Subsequent content that FDA recommends be placed under this heading includes…	Clarify that placement of this information be at the most appropriate point in the administration process (e.g., if taking one hour prior to eating, information should be presented before administration process is started) and that this information is only needed when time and activity are a part of the dosing regimen.	Rationale included within proposed change.
274-286	• Safety information or other important instructions specifically related to administration…	Include the following "subsequent content" in the safety information section of the Draft Guidance: • Warnings or precautions to be taken that need to be brought to the immediate attention of user of the product; for example: - This product is a single-use product and should not be re-used. - This product is provided sterile through an ethylene oxide process. The sterile state of the product is indicated by a sealed package. DO NOT USE if the seal is broken. - Warnings, precautions and/or measures to be taken if the device constituent part of a combination product malfunctions or changes in its performance that may affect the product's safety or efficacy, including reporting of said malfunction to the manufacturer or distributor of the product.	Clarifies how specific regulatory requirements for labeling (specifically, the EU Medical Device Regulation requirements of the content of the Instructions for Use) can be addressed within the framework of this FDA guidance.

Line Reference	Draft Guidance Text	Proposed Revision/Comment	Rationale
		- Instructions under what circumstances should a lay person consult a healthcare professional	
282-286	• Instructions to prevent or mitigate the risk of secondary exposure to a drug...	Emphasize with highlighting or boldface. Also recommend adding that a warning should be provided to users to avoid specific behaviors if the applicant suspects or has been informed that these behaviors have the potential for secondary exposure.	Consider menopausal hormonal therapies such as those applied as a spray to the inside of the forearm which have caused unintended consequences although the exact wording provided in the example on lines 284-286 was used in the IFU; in the case of Evamist® (estradiol transdermal spray), women who used this therapy unknowingly transferred the drug to children and pets.
293	**Preparing to [Insert Applicable Action Verb][Insert Drug Name]**	Change highlighted to: **Before using [Insert Applicable Action Verb][Insert Drug Name]**	Clarifies when this set of instructions should be performed.
303-311	• Information about supplies and materials… • Information about the amount of time… • Instructions to check the drug product…	The Draft Guidance should recommend that this information be placed in the IFU to optimize users' work flow. For instance, "checking that the drug in a vial is not discolored" would be best completed before "waiting 30 minutes for it to warm up," so that the user can save themselves 30 minutes if the drug was faulty.	Rationale included within proposed change.
311	Instructions to check the drug product for particles or discoloration…	Add highlighted: Instructions on how to check the drug product for particles or discoloration	The patient or caregiver may not know what to check for or how to check.
314-324	• Directions for assembling parts or components of the product…	Reduce the number of points included before the user gets to the main administration instructions.	Avoids relating these points with the main administration steps. Providing information at the point of need avoids repetition or confusion in the sequence of use steps.
338-339	FDA recommends that information appear as logically ordered, detailed, step-by-step instructions so that patients…	Add highlighted: FDA recommends that information appear as logically ordered, detailed, illustrated, step-by-step instructions, so that patients…	Complements the more detailed recommendations for illustrations found in Section IV.B.2 of the Draft Guidance.
349, 355	body prep/injection site rotation	Relocate these step(s) from the Administration section to the Preparation section.	Focuses the Administration section more on the actual use of the device.

Line Reference	Draft Guidance Text	Proposed Revision/Comment	Rationale
353-363	• Instructions…	For each of these five bullet points, add "and illustrations" after the word "Instructions."	Aligns with lines 68-72 (visual instructions).
365-385 & Appendix 631-632 386-415	*8. Storage Instructions* (8) **Storing [Insert Drug Name]** *9. Disposal Instructions*	Consider relocating storage information from after drug administration and just before disposal to earlier in the IFU, perhaps after **Important Information You Need to Know Before…** or in a separate section, based on the product task analysis. Move disposal instructions to appear immediately after administration instructions (e.g., by including as a sub-header under *After Your Injection*).	Instructions should align with the sequence of use. Particularly for single-use products, storage is unlikely to occur just before disposal (e.g., patients would store the product as soon as they get home). For example, if the product needs to be refrigerated, the patient might not realize until after the drug has been administered. Conversely, instructions to immediately dispose of single-use products like a used needle should appear immediately after administration.
Footnote 24	Appropriate language to include for safe sharps disposal is available at www.fda.gov/safesharpsdisposal.	Recommend providing more guidance on the appropriate language for safe sharps disposal and shorter text that can be copied and pasted into IFUs. If the suggested language does not fit within the IFU panel, allow the full information to be listed in a Helpful Tips section and reference information within the step language.	Location of appropriate language within website is unclear. Text proposed by FDA is very long. Approach would provide the information to the user only when the user needs to know it.
419	…following information be placed…	Add highlighted: …following information included in the Prescribing Information be placed…	To ensure that the information in the IFU matches that in the PI.
423-424	…(for example, a telephone number that patients can call to speak with a customer service representative).	Change to: … (for example, a telephone number for adverse event reporting or appropriate company contact information).	Provides additional resource options and more flexibility for sponsors to provide means for contact.
447-450	Formatting has a large effect…	Add to end of paragraph: "Recommendations are applicable regardless of IFU presentation (e.g., leaflet, booklet)."	Emphasizes that formatting requirements are universal across all IFU types.
456-458	FDA recommends using a sans-serif font…	While the recommendation to use a sans serif font similar to that of PI and other patient labeling is good, delete the names of these fonts (Verdana and Arial).	Graphic designers understand the difference between serif and sans serif and will select the appropriate font based on standards for

Line Reference	Draft Guidance Text	Proposed Revision/Comment	Rationale
			labeling, container labels, and carton labeling.
464	…font size be no smaller than 10 points…	Rather than point size, specify a minimum font height/size using the correct typographic nomenclature (ascender, descender, stem height, x height, cap height, median height, etc.).	Point size is not an absolute, as it varies from font to font.
486-492	FDA recommends that the following information appear in bold type…	Replace "in bold type" with "with increased prominence."	Choice of visual mechanism to achieve prominence should be left to the applicants' design judgment. Bold text interspersed into regular format text is not recommended because it can cause users to jump ahead in bodies of text, and be distracted by emboldened key words, causing users to mentally reassemble the instruction in an incorrect or confusing way.
503-504	…(for example, "check appearance of liquid following reconstitution")…	Replace "check" with words associated with a defined action that has a resultant outcome, such as discarding faulty product, or providing reassurance that a positive observation means it is safe to continue.	Rationale included within proposed change.
517-518	If a patient needs to repeat a step or steps…	Recommendation should allow for the option of restating of an action rather than forcing the user to navigate the document.	Restatement may be easier and simpler.
526-527	**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."	Replace "skip to Step 8" with "go on to Step 8."	No "skip" is required to move from Step 7 to Step 8.
Footnote 25	For information on visuals and critical tasks…	Replace or append the referenced draft guidance with another that includes information about visuals.	The referenced guidance does not include any information on visuals.
542-544	The Agency also recommends that visuals be labeled…	Replace recommendation to label figures with clearly associating the image with the related text.	Adding and referencing these labels adds extra words on the page which may discourage users from reading the IFU. Figures should not generally need to be

Line Reference	Draft Guidance Text	Proposed Revision/Comment	Rationale
			labeled if a stepwise construct is used or if the figure is placed close to the IFU step.
557-558	…FDA recommends adding a single line before each heading).	Relocate this recommendation to the section on headings (line 114).	Co-locate the information with headings to ensure it is easily found within the Draft Guidance.
558-560	To aid in reading ease, FDA suggests using white space between blocks of text…	Recommend avoiding blocks of text where possible.	Allows low literacy (and other) readers to fully assimilate the message, particularly where mitigation follows actions. White space can be used to manage this effectively.
624-625	(5) Important Information You Need to Know Before [Insert Applicable Action Verb] [Insert Drug Name]	Remove the drug name throughout the IFU except at the start of the instructions.	The drug name should be inserted sparingly because the extra text may make the IFU look cluttered and difficult to read, especially in the titles summarized in the Appendix (line 624 to 633).