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FDA-2017-D-0154

VIA ELECTRONIC SUBMISSION

May 19, 2017

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

Re: Docket No. FDA-2017-D-0154: Considerations in Demonstrating Interchangeability with a Reference Product

Dear Sir or Madam:

The Combination Products Coalition ("CPC")[1] welcomes the opportunity to offer comments on FDA's "Considerations in Demonstrating Interchangeability with a Reference Product: Draft Guidance for Industry" ("Draft Guidance").[2] Overall, the CPC believes that the Draft Guidance is a positive step forward in clarifying the approval pathway for interchangeable biologic-device combination products. However, as detailed below, the CPC has significant concerns surrounding the Draft Guidance. We hope that FDA will consider our comments as it finalizes its guidance, and works toward providing a balanced and sustainable pathway to market for interchangeable biologic combination products that both protects patient safety and allows for innovation that can improve user experiences.

While the CPC agrees with many of the recommendations in the Draft Guidance, we strongly recommend that FDA revise the document to:

1. Improve alignment between the Draft Guidance and existing human factors ("HF") guidance provided by FDA and by recognized U.S. and international standards;
2. Focus comparative analyses on risk, not use error rates;

[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.

[2] We note that many of the comments included here mirror those that the CPC submitted on FDA's "Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry."

3. In accordance with item 1, describe HF studies as qualitative research (to assess the adequacy of the product user interface) rather than quantitative research (to assess the capabilities of the users);
4. Promote innovation and improvements to the design of products to enhance safety and effectiveness; and
5. Provide more information regarding topics not sufficiently addressed in the Draft Guidance.

We have also included additional, specific comments in Appendix A.

I. Improve Alignment between the Draft Guidance and Existing HF Guidance Provided by FDA and by Recognized U.S. and International Standards

To enable a consistent HF engineering approach, the CPC strongly recommends that FDA align the Draft Guidance with previous FDA HF guidance documents[3] and FDA-recognized consensus standards.[4] Previous FDA HF guidance offers input on the "appropriate human factors and usability engineering processes to maximize the likelihood that new medical devices will be safe and effective for the intended users, uses and use environments."[5] Specifically, these guidance documents describe a risk-based approach for analyzing a product's user interface, identifying the critical tasks, and conducting HF evaluations to assess potential use errors on the critical tasks that could impact safe and effective use. In addition, FDA-recognized consensus and internationally harmonized standards provide guidance on managing use-related risks for medical devices and implementing a rigorous HF engineering process.

One specific area where FDA can improve alignment between these documents and standards and the Draft Guidance is in its use of terminology. For example, FDA introduces in the Draft Guidance the term "external critical design attributes," which it defines as "features that directly affect the performance of critical tasks that end users perform to appropriately use or administer the product" (lines 702-704). We find this term problematic because some design attributes are not "external," but they impact device use nonetheless. For instance, spring force, which is an internal design attribute, impacts the injection time of an autoinjector. The use steps associated with the injection are considered critical tasks in the administration of the drug.

To improve consistency and avoid confusion, we recommend that the Draft Guidance instead use the term "primary operating functions," which is defined in IEC 62366:2015 as a "function that involves user interaction that is related to the safety of the medical device." Using this term in the Draft Guidance, rather than FDA's proposed term, can serve FDA's purpose

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[3] FDA, CDRH, *Applying Human Factors and Usability Engineering to Medical Devices: Guidance for Industry and FDA Staff* (2016) ("HF/Usability Engineering Guidance"); FDA, *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development: Draft Guidance for Industry and FDA Staff* (2016) ("Combination Product HF Draft Guidance").

[4] See e.g., AAMI/ANSI HE75:2009, *Human factors engineering – Design of medical devices*; IEC 62366-1:2015, *Medical devices – Part 1: Application of usability engineering to medical devices*; ISO 14971:2007, *Medical devices — Application of risk management to medical devices*.

[5] HF/Usability Engineering Guidance at 1.

while facilitating sponsors' ability to comply with international standards as well as FDA's expectations.

II. Focus Comparative Analyses on Risk, Not Use Error Rates

The Draft Guidance provides two categories for external critical design attributes: "minor" and "other (non-minor)" (lines 786-821). The only difference between the two categories is whether the difference in user interface would affect a primary operating function. The problem with this approach is that it would lead to the definition of "other differences" being too broad (lines 803-807).

Using a prefilled syringe ("PFS") as an example, "remove syringe needle cover" is identified as a critical task per the Combination Product HF Draft Guidance. Therefore, under the Draft Guidance, the needle cover itself would be considered an "external critical design attribute." By extension, any design differences in the needle cover, even the color, would then be considered an "other (non-minor)" difference and may require a comparative HF study. This results in a mischaracterization of risk and ultimately, an undue burden on the sponsor of the proposed interchangeable biologic.

Instead of assessing differences in a binary fashion (impact or no impact), we recommend that the Draft Guidance utilize a tiered approach based on a risk assessment of the proposed interchangeable product. For example, AAMI ANSI ISO 14971 provides an example of qualitative severity levels (catastrophic, critical, serious, minor, and negligible), as well as the definitions for each. We recommend that the impact of differences in the user interface be assessed in a similar fashion, i.e., based on the risk analysis of the proposed interchangeable product.

We understand FDA's concern about the potential for the proposed interchangeable product to introduce use errors that could result in serious harm. And we believe that a side-by-side analysis of the proposed interchangeable product presentation and the reference product presentation, as the Draft Guidance suggests, can be helpful in examining the risk of medication errors for the interchangeable product. However, we ask that FDA include the following in the threshold analysis to provide additional clarity and specificity:

- Differential task analysis – What are the tasks (and sub-tasks) for using each device that differ between the proposed new product and the reference product? This analysis should be sufficiently granular such that differences in user interface, such as differences in primary operating functions, are detected. For example, differences in the specific action(s) a user would take to activate an autoinjector should be listed individually (e.g., push on skin and press activation button), and not lost under a general "Activation/Dose Delivery" task.

- Use error analysis – What use errors could the user make while performing these tasks with the proposed interchangeable product? What use errors could the user make that are a direct result of the differences between the new product presentation and the reference product presentation, e.g., due to familiarity with the reference product and negative transfer of learning from the reference product to the new product?

- Severity analysis – What could be the consequences of each of the use errors that the user could make with the proposed interchangeable product? The results would be used to identify the critical tasks of use (i.e., those tasks that if performed incorrectly or not at all could result in serious harm).

The results of the analyses listed above would enable identification of the criticality of the differences between the new product and the reference product presentations, which would determine whether HF testing would be needed to assess those differences. The added components to the threshold analysis would also help in taking into consideration the possibility that patients familiar with use of the reference product may be at risk when switched to the proposed interchangeable without the intervention of the prescribing physician. If testing is necessary, the HF testing should then focus on those tasks for which the use-related risks are different from those of the reference product presentation, and on which use errors associated with the differences in product design could result in serious harm. Such testing could either be conducted separately from or in conjunction with the standard HF validation testing proposed for a new product.

We recommend that this testing not include user testing of the reference product as assessment of the reference product has already been carried out through the previously described differential task analysis, and post-market safety reporting could be problematic, as described in the next section. The goal of the HF testing is to ensure that the intended users of the proposed interchangeable product can use the product safely and effectively, even if some of the design elements differ from those of the reference product.

III. Describe HF Studies as Qualitative Research (to Assess the Adequacy of the Product User Interface) Rather than Quantitative Research (to Assess the Capabilities of the Users)

The CPC has concerns regarding the non-inferiority ("NI") inter-device comparative study design approach described in Appendix A of the Draft Guidance, and proposes a different approach. HF validation studies are designed (as explained in IEC 62366-1:2015 and FDA's HF/Usability Engineering Guidance) as studies where understanding the root cause of a participant's use error is as important as the fact that it occurred. Percentages of successful use and use error rates are less important than detecting use errors that could result in serious harm, regardless of how infrequently they occur, or even if they occur only once in the study. The number of use errors that occur when using a device does not provide evidence, either positive or negative, about the safety or effectiveness of that device unless the potential consequences of those errors are also analyzed.

In its 2015 update of IEC 62366 (now designated as IEC 62366-1), the international committee that wrote the standard removed the acceptance criteria that were included in the first (2007) edition specifically for this reason. For the same reason, the phrase "pattern of use error" was removed from the draft version of the HF/Usability Engineering Guidance when it was finalized in 2016. Requiring a NI approach, based on principles used in placebo-controlled clinical trials of medicinal products, and in this case comparing use error rates, is not appropriate for assessments of user interactions with a user interface, especially where (multiple) different types of use errors could result in different severities of harm.

The Draft Guidance states that the goal of HF studies in this circumstance is to ensure that the intended users can use the proposed interchangeable product "without the intervention of the prescribing health care provider or additional training…" (lines 683-684). We believe that this goal can be achieved more meaningfully with a threshold analysis and a standalone HF study on the proposed interchangeable product, rather than a quantitative, statistically powered non-inferiority comparative use HF study on the proposed new product and the reference product.

The evidence needed to prove the safety of switching a patient to a proposed interchangeable product can and should be generated using standard HF engineering methods for these products without testing of the reference product. We believe that the most appropriate study design would be to test two user groups in the study of the proposed interchangeable product: (1) users who are familiar with the reference product presentation (and possibly other similar reference product presentations), and (2) users who are naïve to the product category. Training would not be provided to those users familiar with the reference product presentation. Training would only be provided for naïve patients as appropriate per the label if they were receiving the product for the first time. Both groups would be provided the instructions for use, but not required or asked to read them; and the results would show whether these users could use the proposed interchangeable product presentation safely and effectively without intervention of a health care provider or additional training. We believe this study design directly addresses FDA's concerns regarding the risks associated with switching users from the reference product to an interchangeable product alternative.

Finally, with respect to the study design proposed in the Draft Guidance, we have concerns about the post-market safety reporting that would be required if the reference product is tested by the proposed interchangeable product applicant. Our concern is that the Draft Guidance does not explain FDA's expectations for reporting use-error complaints and/or malfunctions of the reference product that occur during such HF testing. Our proposal above, which precludes testing of the reference product in the HF validation study of the new product would avoid this concern, and is therefore our preferred approach.

IV. Promote Innovation and Improvements to the Design of Products to Enhance Safety and Effectiveness

The Draft Guidance notes that "FDA generally encourages optimization of the design of the delivery device constituent part to enhance safety of the product" (FN 35). The CPC acknowledges and agrees with the flexibility provided in the Draft Guidance to promote innovation. In addition, we recommend that FDA apply a risk-based approach to HF assessments to justify improvements that reduce the residual risks associated with use of the product. This approach would apply to the design of the labeling (especially the instructions for use). There is no benefit to the patient in replicating suboptimal instructions solely for the purpose of not being different. The approach would also apply to other items of labeling, such as training materials (e.g., videos, handouts, checklists, and training simulators).

V. Provide More Information Regarding Topics Not Sufficiently Addressed in the Draft Guidance

We also recommend that FDA provide additional guidance with respect to handling: (1) post-approval changes to the reference product presentation, (2) reference products with multiple presentations, and (3) labeling issues related to patient training.

A. Post-Approval Changes to the Reference Product Presentation

The Draft Guidance focuses on a comparison of the proposed interchangeable product to the reference product presentation at the time of application. However, there will likely be design changes to the delivery device of the reference product over time. The Draft Guidance does not address how the proposed interchangeable product applicant should handle such changes to the reference product presentation in the future or how to handle situations where the user interface design of the interchangeable product and the reference product diverge over time.

Product divergence presents a distinct risk for patients who may be switched between the reference product and the interchangeable product, because new risks resulting from divergence would not have been addressed by the original comparison. Additionally, the original comparison may "lock in" one or both parties (the interchangeable product or reference product applicants) to the design at the time of application, instead of allowing the opportunity for continuous improvement and innovation over time to enhance patient safety and the user experience. Therefore, the risk of divergence should be balanced against the benefit of product improvement.

We ask that FDA revise the Draft Guidance to explain expectations on reference product and interchangeable product manufacturers when there is a change in the reference product presentation (e.g., design change, software updates, etc.). The Draft Guidance does not specify the mechanism for notification of such change, or whether a new analysis would have to be conducted and submitted to FDA. We recommend that following approval, changes to the design of any individual product be handled independently under existing guidance.

B. Reference Product with Multiple Presentations

We also ask that FDA update the Draft Guidance to explain expectations when a reference product is approved for use with multiple presentations of delivery devices, particularly where the sponsor of the proposed interchangeable is seeking approval with fewer presentations than those that are available for the reference product. For example, when a reference product is available in both a PFS and a prefilled autoinjector, and the interchangeable product is only available in a PFS, it is very likely that when a physician prescribes the reference product in an autoinjector, the pharmacy would choose to dispense the interchangeable product in a PFS. In such a scenario, the comparative analyses as described in the Draft Guidance and as proposed in the comments above may not be sufficient to assess interchangeability of the reference product and proposed interchangeable product.

Additionally, differences in the reference product and interchangeable product presentations may very well occur due to life-cycle management activities by the reference product manufacturer, such as significant design changes or the removal and/or addition of

presentations (e.g., enhancements to a prefilled autoinjector that improve the usability of the product, or retiring a co-packaged presentation with a vial and empty syringe in favor of a PFS presentation).

The Draft Guidance states, "A sponsor developing an interchangeable product generally should not seek licensure for a presentation for which the reference product is not licensed" (lines 653-655). It further provides, "A sponsor planning to develop a presentation for which the reference product is not licensed should discuss its proposed presentation with FDA" (lines 657-659). As the applicant would be proposing a device with a new user interface, this product should follow the approaches set out in FDA's previous HF guidance documents (i.e., the HF/Usability Engineering Guidance and the Combination Product HF Draft Guidance). We recommend that FDA reference these documents with respect to the approach to be taken in this situation.

C. Labeling

Most biologic manufacturers have recognized the need for patient training and have explicitly stated in their approved prescribing information (in Section 17 Patient Counseling Information) that physicians or other health care providers should: (1) evaluate each patient's ability to administer the medication, (2) provide training to patients on medication administration, and (3) observe patients while they are performing their first injection. The need for training is also stated in the approved Medication Guides for most reference biologics as well as in the approved patient instructions for use. Presumably, the label of a proposed interchangeable biosimilar will include the same statements; however, the Draft Guidance does not explain how a biological product, with this labeling, "may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product" (emphasis added) (line 686-687). Although the issue of substitution without health care provider intervention or training is discussed in Section VIII B (lines 678-690), the Draft Guidance does not consider situations where the practice of substitution without health care provider intervention would be contrary to the approved labeling, or address how this labeling restriction impacts interchangeability. We ask that FDA provide further guidance on these points.

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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 suggested revisions.

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
676-678	"The design of the presentation determines the specific tasks necessary to administer the product. These tasks can vary considerably depending on the type of presentation and its design characteristics."	Add examples of preliminary analyses that should be performed as part of the design and development process of the proposed interchangeable product. The paragraph should read as follows: "The design of the presentation determines the specific tasks necessary to administer the product. These tasks can vary considerably depending on the type of presentation and its design characteristics. **When developing the presentation, sponsors should consider performing preliminary analyses, such as heuristic analysis, identification of known use problems, etc.**"	The Draft Guidance does not identify whether any preliminary analyses (e.g., heuristic analysis, identification of known use problems, etc.) are recommended, as identified in the HF/Usability Engineering Guidance. For example, new use-related problems may have come to light between approval of the reference product and development of the proposed interchangeable product. We ask that FDA reference the applicable preliminary analyses.
678-684	"Differences in the design of the container closure system or delivery device constituent part between the proposed interchangeable product and the reference product may be acceptable provided that the design differences are analyzed appropriately and data are provided to demonstrate that the changes do not negatively impact the ability of end users, including patient and caregiver end-user groups, to appropriately use these products when	Add risk assessment as part of the analysis, and a reference to residual risk related to usability. The paragraph should read as follows: "…without the intervention of the prescribing health care provider or additional training before use. **Differences should be justified according to risk assessment, and result in acceptable residual risk related to the usability and use-safety of the product.**"	A sponsor should follow a systematic risk assessment approach to analyze the difference(s) in user interface between the proposed interchangeable product and the reference product. The acceptability of design differences from an HF perspective should be based on the acceptability of residual risks related to the usability and use-safety of the product.

Line Reference	Draft Guidance Text	Proposed Revision/Comment	Rationale
	the interchangeable product is substituted for the reference product without the intervention of the prescribing health care provider or additional training before use."		
FN 32	"The user interface also includes the delivery device constituent part labeling…"	Add "packaging" to the sentence so that it reads: "The user interface also includes the delivery device constituent part **packaging** and labeling…"	For completeness, packaging should be included as it is part of the product user interface.
735-739	"As a result, there is concern that patients or caregivers who encounter different external critical design attributes between the container closure system and/or delivery device constituent part of a reference product and a proposed interchangeable product may be at increased risk for a use-related error that may impact their ability to appropriately use these products."	Replace "differences in external critical design attributes" with "user interfaces," and replace "appropriately use these products" with "perform critical tasks" so that the paragraph reads: "As a result, there is concern that patients or caregivers who encounter different **user interfaces** between the container closure system and/or delivery device constituent part of a reference product and a proposed interchangeable product may be at increased risk for a use-related error that may impact their ability to **perform critical tasks**."	The Draft Guidance defines "external critical design attribute" in the context of ability to perform critical tasks. We recommend highlighting the ability to perform critical tasks to ensure clarity.
748-750	"FDA recommends a side-by-side, line-by-line comparison (between the reference product and the proposed interchangeable product) of the full prescribing information, instructions for use…"	Remove prescribing information from the list or consider rewording to note aspects of the prescribing information that impact usability and use-safety.	Most of the prescribing information content is outside the scope of HF and the usability and use-safety of the product.
780-784	"If differences are identified between the design of the presentations of the proposed interchangeable	Clarify that risk analysis should be used to assess the potential impact of the differences in the user interfaces. The paragraph should read as follows:	The acceptability of the differences in the product user interfaces should come back to critical tasks, potential

Line Reference	Draft Guidance Text	Proposed Revision/Comment	Rationale
	product and the reference product, the sponsor should focus on whether the difference(s) involves an external critical design attribute that can negatively impact appropriate use by the patient and caregiver end-user groups…"	"If differences are identified between the design of the presentations of the proposed interchangeable product and the reference product, the sponsor should focus on whether the difference(s) **may impact a critical task, hence the usability and use-safety of the product as it relates to that task. A risk analysis consistent with ISO 14971:2007, *Medical devices — Application of risk management to medical devices* and FDA guidance, *Applying Human Factors and Usability Engineering to Medical Devices*, is suggested**."	use errors, and an analysis of use-related risk.
786-788	"FDA views a design difference in product presentation as minor if the differences in the user interface of the proposed interchangeable product, in comparison to the user interface of the reference product, do not affect an external critical design attribute."	As noted in the body of this document, we recommend coupling a differential task analysis along with a use error analysis and severity analysis to assess the criticality of use-related risks. This should be the basis to determine the impact of differences in primary operating functions and enables a level of granularity in the analysis with which to base the need for HF testing.	The use of primary operating functions and risk analyses to assess the impact of product differences is consistent with existing FDA HF guidance and recognized standards.
807-808	"In such cases, the sponsor may consider modifying the design of the proposed presentation to minimize differences from the reference product, which could reduce the data that might be needed to support a demonstration of interchangeability."	Replace "modifying the design of" with "designing." The sentence should read as follows: "In such cases, the sponsor may consider **designing** the proposed presentation to minimize differences…"	Consistent with feedback in text above.
845-847	"The objective of the comparative use human factors studies described	Focus the comparative use HF studies on the residual risks of the proposed interchangeable product.	FDA's HF guidance and recognized consensus standards

Line Reference	Draft Guidance Text	Proposed Revision/Comment	Rationale
	in this guidance is to assess any differences in the use error rate between the reference product and the proposed interchangeable product."	The paragraph should read as follows: "The objective of the comparative use human factors studies described in this guidance is to **<u>demonstrate that the residual risk related to use errors associated with the proposed interchangeable product is acceptable, and in particular to assess whether there is risk for patients switched between the reference and interchangeable products without the intervention of the prescribing health care provider</u>**."	recommend not calculating use error rates, but focusing on the root cause of observed errors and associated risks.
994-1033	Sample Size Considerations	The sample size described in this section does not align with FDA's HF/Usability Engineering Guidance, which states the following (p. 36): "Since the parameters needed to determine sample size cannot be estimated easily or cannot be at estimated at all prior to testing, a sample of 15 people to detect most of the problems in a user interface constitutes a practical minimum number of participants for human factors validation testing. This sample size theoretically provides the best possibility of detecting user interface design flaws while limiting the amount of resources required…"	Align text with previous FDA guidance. The described NI study design sample size would be overly burdensome for an interchangeable product applicant, especially considering the inability for such a study to fully address the question of interchangeability risks.