Combination Products Coalition

1227 25th St. NW #700
Washington, DC 20037
combinationproducts.com
202.861.4199

FDA-2018-D-3275

**VIA ELECTRONIC SUBMISSION**

November 30, 2018

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

Re: Docket No. FDA-2018-D-3275: Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications: Draft Guidance for Industry and FDA Staff

Dear Sir or Madam:

The Combination Products Coalition ("CPC")[1] welcomes the opportunity to offer comments on FDA's "Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications: Draft Guidance for Industry and FDA Staff" (hereinafter "Draft Guidance").

Overall, the CPC believes the Draft Guidance represents a positive step forward in clarifying FDA's expectations for these types of human factors ("HF") submissions in relation to the specific application pathways for 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 However, as detailed below, the CPC has significant concerns surrounding the Draft Guidance.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 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While the CPC agrees with many of the recommendations in the Draft Guidance, we strongly recommend that FDA revise the document to: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. Provide clear guidance and delineation as to which HF tools are applicable to which types of submissions/situations.

[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. Request that sponsors only provide representative samples of their own product for certain submission types and remove the request for samples of competitors' reference products.

In addition, we request that FDA take into consideration past comments on referenced guidance documents that also apply to this Draft Guidance, including recommendations to:

3. Improve alignment between the Draft Guidance and existing final HF guidance documents issued by FDA and FDA-recognized U.S. and international standards.
4. Focus comparative analyses on risks, not use error rates.
5. In accordance with item 3, 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).

Items 3, 4, and 5 above are consistent with comments provided previously by the CPC regarding FDA's draft HF guidance documents related to ANDA submissions[2] and interchangeability with a reference product[3] (see docket numbers FDA-2016-D-4412 and FDA-2017-D-0154 for additional details).

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

**1. Provide clear guidance and delineation as to which HF tools are applicable to which types of submissions/situations**

We request that the Draft Guidance identify which HF submission type is applicable to which application pathway. This is currently ambiguous within the document, which could result in the Agency receiving unnecessary submissions. For example, FDA should clarify within the Draft Guidance that threshold analysis and comparative analysis are only applicable to generic products under an ANDA or interchangeable biosimilars, as identified within the ANDA HF Draft Guidance and the Interchangeability Draft Guidance. In order to ensure consistency between the Draft Guidance and other draft FDA HF guidance documents, we recommend removing the corresponding information from this Draft Guidance and placing it in the relevant existing guidance documents. For example, the Agency could remove the submission information related to threshold and comparative analysis, and place this in the ANDA HF Draft guidance and Interchangeability Draft Guidance. This would ensure all the necessary information is in one location and ensure clarity on what is required for each application pathway.

There are also opportunities for the Agency to improve alignment in scope between the Draft Guidance and existing draft FDA guidance documents, including the Combination Product

[2] FDA, Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry (2017) ("ANDA HF Draft Guidance").

[3] FDA, Considerations in Demonstrating Interchangeability with a Reference Product: Guidance for Industry (2017) ("Interchangeability Draft Guidance").

HF Draft Guidance.[4] The scope of these previous guidance documents has been identified as being applicable to combination products as defined under 21 CFR Part 3 when CDER/CBER is the lead FDA Center, while the Draft Guidance refers to "Human prescription drugs, including biologics," which do not necessarily include a device. This represents a significant change in scope.

The intent of the Draft Guidance, as identified in its introduction, is to provide "guidance to industry and FDA staff on the contents of and submission procedures for threshold analyses and [HF] submissions," and therefore not to identify new expectations. We recommend aligning the scope of the Draft Guidance with the scope of the previous FDA HF guidance documents (including those referenced in footnotes 2 through 4) to prevent misinterpretation of FDA's expectations, which could result in unnecessary HF submissions. This alignment would ideally be achieved by moving the relevant information from this Draft Guidance to the other draft guidance documents, as discussed previously.

We also have concerns around the Draft Guidance's approach to "Use-Related Risk Analysis," which is one of the HF submission types discussed in the document. ISO 14971:2012 defines risk analysis as the "systematic use of available information to identify hazards and to estimate the risk." However, the use-related risk analysis approach detailed within Section IV.A of the Draft Guidance (lines 110 to 151), and the associated example in Appendix B, do not identify risk estimation as a requirement within this submission type. Further, the wording in the Draft Guidance implies that a full use-related risk assessment needs to be submitted with the HF validation study report; in contrast, the HF/UE Guidance[5] advises: "[For analysis of hazards and risks associated with use of the device]...provide an excerpt from the comprehensive risk analysis that contains all the use-related hazards and risks, including those associated with potential use errors."

Also, it may be overly burdensome for sponsors to provide information on validation for mitigation strategies for all use-related risk analysis submissions. For example, an extractable and leachable study may not warrant submission of protocols for validation methods. We recommend that FDA identify this submission type as something other than a "Use-Related Risk Analysis" – for example, a "Hazard Analysis" or "Risk Assessment Summary." In order to prevent sponsors from submitting full Use Failure Modes Effects Analyses ("FMEAs"), we also recommend that FDA specifically state within this Draft Guidance that a Use FMEA is not required to be submitted as part of a Use-Related Risk Analysis or HF Validation Study Report submission type.

Next, we appreciate the inclusion of the timeline for FDA review of HF Validation Protocols and HF Validation Reports in the Draft Guidance, though we suggest that timelines also be provided for the other HF submission types. For example, if a "Use-Related Risk Analysis" submission concluded that a HF validation study is not required and there was no review response timeline, the sponsor would need to continue the project at risk. If this conclusion was rejected by

[4] 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").

[5] FDA, Applying Human Factors and Usability Engineering to Medical Devices: Guidance for Industry and FDA Staff (2016) ("HF/UE Guidance").

FDA and came late in the development process, it could result in a significant change in approach for the sponsor, resulting in a delay of the application submission. This delay would be caused by the sponsor needing to plan the study, generate and submit the HF Validation Study Protocol, and wait for another FDA review. Having a guideline review timeline for all submissions would allow sponsors to adequately plan for each of these submission types.

**2. Request that sponsors only provide representative samples of their own product for certain submission types and remove the request for samples of competitors' reference products**

We recognize the value FDA sees in sponsors providing samples of their proposed product as part of certain HF submissions, and also appreciate FDA's recognition in the Draft Guidance that provision of these samples may not be feasible in all cases. We further appreciate the Agency's willingness to discuss the situation with sponsors in such instances, which we expect may be frequent.

One reason the provision of to-be tested and intend-to market samples to FDA might not be feasible is that sponsors submit threshold assessments at a point when they are attempting to determine if submission of an ANDA is possible. As many of the suggested mitigations for more than minor differences is a redesign of the product, it is not reasonable for a company to invest significant resources to produce a set of final products. In many cases, a few prototypes are available that may not have all of the characteristics that will be implemented in the final product. For that reason, samples should not be required to accompany threshold assessments. Another reason for this is that sponsors submit HF protocols far enough in advance of finalizing the test materials to ensure that the protocol will have been reviewed and FDA feedback incorporated in time to conduct the HF validation study and meet planned application submission deadlines. In the case of intend-to market samples, final printed labeling (e.g., USPI) may not be available until after label negotiations are complete and language is final.

In order to minimize the need for discussion with FDA on this topic, we request that the Draft Guidance provide additional options with regard to the types of samples that might be acceptable. For example, we believe there are other items that could be supplied by the sponsor that might be useful for FDA review purposes (e.g., prototype samples sent along with a clear explanation of the differences between such samples and the to-be tested/intend-to market samples). This would provide the reviewer with a greater understanding of the product and its user interface.

Further, in order to facilitate efficient provision of these samples, FDA should provide additional information on how best to accomplish this task. For example, we ask that FDA provide a physical address to which the samples should be sent and explain any packaging and labeling requirements for such samples, as they could contain an investigational/unapproved drug. FDA should also explain how these samples will be used and if there are any limitations on how such products will be used. For instance, will the samples be used only to evaluate the user interface and not be tested for any analytical or clinical properties of the drug product?

In addition, we note that the Draft Guidance recommends five product samples (i.e., five samples of product that will be tested in the HF validation) for different types of analyses. As

there may be more than one similar presentation planned under the same HF study, we ask that FDA confirm the number of samples that should be submitted if different, but similar presentations are planned under the same study protocol. For example, if two or three different presentations are planned under the same HF protocol, it would be helpful for FDA to clarify whether the sponsor should submit five samples total under the protocol, or five samples for each of the presentations. It may be more practical to specify five samples in total for a study, rather than five of each.

Finally, the provision of sample reference product for comparative use HF studies would no longer be required if the approach described in Section 5 of this comment letter is adopted. Provision of samples of product not owned by the sponsor could lead to legal challenges with regard to the sponsor representing a competitor's product as well as shipment of a possibly controlled substance outside of the sponsor's direct control.

**3. Improve alignment between the Draft Guidance and existing final HF guidance documents issued by FDA and FDA-recognized U.S. and international standards**

To enable sponsors and FDA to follow a consistent HF engineering approach, the CPC strongly recommends that FDA align this Draft Guidance with previously released FDA HF guidance and FDA-recognized consensus standards,[6] as the addition of a drug component does not change the overall HF approach.

In particular, we recommend that FDA improve alignment in terminology between the released FDA HF/UE Guidance and the Draft Guidance. For example, in the Draft Guidance, the term "critical task" is defined as one that "may cause harm" (line 605), while the HF/UE Guidance defines the term as one that "could cause *serious* harm" (emphasis added). The latter definition allows the product specific hazard assessment and use-related risk assessment to drive the determination of whether a task is critical; this definition is preferred as it aligns with a risk based approach to HF. In addition, the Draft Guidance identifies the "Human Factors Validation Study Report" as equivalent to the report identified in Appendix A of the HF/UE Guidance (per footnote 24 of the Draft Guidance); in the HF/UE Guidance, this report is referred to as the "HFE/UE report." As these reports are equivalent, they should be given the same identifier to promote consistency and make clear that the same requirements apply.

The Draft Guidance also contains a glossary of terms that are not specific to the document itself, which can lead to inconsistencies. To address this, we recommend that FDA follow the same approach used in the FDA Combination Product HF Draft Guidance – i.e., by referring to the glossary in the HF/UE Guidance. Only terminology specific to the Draft Guidance should appear in the document's glossary.

We also note that the definition of "user interface" included in the Draft Guidance (lines 683 to 685) is different from that in the HF/UE Guidance, but aligns with the definitions within IEC 62366-1:2015 and AAMI/ANSI HE75:2009. There should be one aligned set of FDA

[6] 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.

definitions that match those used in the FDA-recognized consensus standards (see footnote 6). A single FDA glossary of terms, aligned to other released guidance documents and standards, would increase consistency across HF submissions. Other specific examples of where consistency can be improved are detailed within Appendix A below.

We also recommend that FDA align the terminology used in the Draft Guidance with other draft HF guidance documents. For example, the term "reference listed drug" ("RLD") is used consistently throughout the ANDA HF Draft Guidance, but in this Draft Guidance, various terms are used, e.g., "listed drug" (line 59) and "product it references" (line 295).

In addition, we note that a request for discussion of residual use-related risks versus benefits of the product is identified as an element to be included in the HF Validation Study Report. However, this has potential for confusion with the overall risk benefit analysis of the product, as defined within ISO 14971, based on all the risks associated with the product and not just the use-related risks, which is part of the risk management file (which includes input from the HF validation study). We request that FDA provide further explanation of this expectation.

Further, the recommendation in the Draft Guidance that HF-related documentation, such as protocols and reports, be placed in Module 5 (as stated on lines 460 to 462) does not align with the ICH M4 which states "module 5 contains the clinical study reports." HF program activities are intended to meet design control requirements as outlined in the HF/UE Guidance, which recommends that "manufacturers consider human factors testing for medical devices as a part of a robust design control subsystem." As HF studies (except for data generated in actual use studies) are not typically clinical studies, Module 3 (i.e., Section 3.2.R Regional Information) is considered a more appropriate location in which to place HF documentation for Agency review.

**4. Focus comparative analyses on risk, not use error rates**

As with other HF activities, comparative analyses, such as threshold analysis and comparative use, should be based on risk. We recommend that the Draft Guidance utilize a tiered approach based on risk assessment of the proposed generic/biosimilar product. For example, AAMI ANSI ISO 14971:2007 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 generic/biosimilar product.

Within the CPC's response to the ANDA HF Draft Guidance, we proposed a threshold analysis approach to improve clarity and specificity on what should be included within this type of analysis. This recommended approach included documenting the tasks required to use the reference device and how these differ from the proposed new product. It also included identification of use errors that could occur when using the proposed new product, as well as the use errors associated with differences between devices and the associated severities of the identified use errors. We recommend that this approach be reflected within the threshold analysis section of the Draft Guidance to promote consistency of submission content for this type of analysis.

The results of the analyses listed above would enable identification of the criticality of the differences between the new product and the reference product, which would determine whether HF testing would be needed to assess those differences. 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, and on which use errors associated with the differences in product design could result in 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 (a) assessment of the reference product has already been carried out through the previously described differential task analysis, and (b) analysis and reporting of use errors made with the reference product and the root cause of the errors would be problematic. The goal of the HF testing is to ensure that the intended users of the proposed generic/biosimilar product can use the product safely and effectively even if some of the design elements differ from those of the reference product.

**5. 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)**

In HF validation studies (as explained in IEC 62366-1:2015 and FDA's HF/UE Guidance), 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 the potential severity of harm that could be caused by the use errors, regardless of how infrequently they occur. The number of use errors that occur does not provide evidence about the safety or effectiveness of the device unless the potential consequences of those errors are also analyzed as part of risk-benefit analysis. Comparing use error rates, (as is described in the Draft Guidance) is not appropriate for assessments of the adequacy of a user interface.

The evidence needed to prove the safety of switching a patient to a generic or biosimilar product 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 generic or biosimilar product: (a) users who are familiar with the reference product (and/or other similar reference products), and (b) users who are naïve to the product category. 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 new device safely and effectively. The number of participants within these study groups would mirror the user group requirements and size detailed within other HF guidance documents and therefore eliminate the need for a statistical sampling plan as this analysis is not related to statistical significance.

The study outlined above falls within the definition of a HF validation study and therefore would not need a separate type of HF submission. We therefore recommend that FDA remove Comparative Use Human Factors Studies as a special submission type and instead include them under the HF Validation submission type. Information related to the FDA's expectation for a Comparative Use Human Factors Study could then be included as a subset of HF Validation Studies, in that section within the Draft Guidance.

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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 |
|---|---|---|---|
| Title | "Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications" | "Contents of ~~a~~ Complete ~~Submission for Threshold Analyses and~~ Human Factors Submissions to Drug and Biologic **Combination Product** Applications" | The title highlights "Threshold Analyses," but it covers Risk Management and HF Validation Protocol review submission guidelines as well. Reference to "combination product" added in line with the comments associated with the scope of the document. |
| 31 | "… referred to *as sponsors."* | "… referred to as *sponsors* **or *applicants***." | As both terms are used throughout this guidance, we recommend clarification to identify that these terms are used interchangeably. |
| 56-58 | "As part of evaluating drug and biologic products for safety and effectiveness, FDA will evaluate HF data submitted by sponsors in support of the product user interface when submission of such data is warranted." | "As part of evaluating drug**-device combination products** and biologic**-device combination** products for safety and effectiveness, FDA will evaluate HF data submitted by sponsors in support of the product user interface when submission of such data is warranted." | User interfaces are only present within combination products with a device element and therefore are not applicable to standalone drug or biologic products. |
| 56-58 | See row above. | The term "HF data'" is not defined. Please provide a definition (for example, all information provided by the manufacturer as described in Section IV) . | Without defining the term, it is not clear what is being referred to. |
| 58-61 | "For products that sponsors intend to submit as an ANDA, the sponsor can rely on the Agency's previous finding that its | "For products that sponsors intend to submit as an ANDA, the sponsor can rely on the Agency's previous finding | The two sentences as currently written are ambiguous as to whether "certain products" refer only to generic products or |

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| | listed drug is safe and effective so long as the sponsor can demonstrate certain findings. Certain products, including drug-device combination products, may warrant threshold analyses and additional data, such as data from comparative HF studies." | that its listed drug is safe and effective so long as the sponsor can demonstrate certain findings. ~~Certain products, including~~ **Generic** drug-device combination products~~,~~ may warrant threshold analyses and additional data, such as data from comparative HF studies." | other types of products as well. As identified within FDA's ANDA HF Draft Guidance, threshold analysis and comparative HF studies are within the scope of generic products. |
| 107-108<br>110<br>153<br>210<br>289<br>313<br>350 | "This section describes the information that a sponsor should include for each respective submission type."<br><br>"Use-Related Risk Analysis"<br>"Human Factors Validation Study Protocol"<br>"Human Factors Validation Study Report"<br>"Threshold Analyses"<br>"Comparative Use Human Factors Study Protocol"<br>"Comparative Use Human Factors"<br>"Study Results Report" | "This section describes the information that **FDA uses to evaluate** ~~a sponsor should include for~~ each respective submission type."<br><br>"Use-Related Risk Analysis **Submissions**"<br>"Human Factors Validation Study Protocol **Submissions**"<br>"Human Factors Validation Study Report **Submissions**"<br>"Threshold Analyses **Submissions**"<br>"Comparative Use Human Factors Study Protocol **Submissions**"<br>"Comparative Use Human Factors Study Results Report **Submissions**" | Proposed revisions provide clarity that requested content should be part of the identified submission type and not part of the actual document referenced in the header for that section. |
| FN 13 | "However, because probability is very difficult to determine for use errors..." | "However, because probability ~~is~~ **may be** very difficult to determine for use errors..." | For certain products that are commonly used and well understood, there may be more knowledge that can be used to determine probability of occurrence of harm (e.g., product complaint databases, clinical and commercial use, usability studies). Therefore, we recommend |

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| | | | updating the language around the difficulty of determining probabilities of occurrence of harm. |
| FN 13 | "Therefore, it may be appropriate when conducting the use-related risk analysis to focus on the resulting harm and including estimated occurrence rates may not be needed." | "Therefore, it may be appropriate when conducting the use-related risk analysis to focus on the resulting harm ~~and including estimated occurrence rates may not be needed~~." | Critical tasks should be defined in terms of reasonable likelihood for a serious harm to occur and including estimated occurrence rates helps provide context for why a task may be defined as critical. Some tasks may have the potential to result in serious harm; however, the risk of harm is remote, and consideration would be impractical (e.g., death by infection as a result of not washing hands or from a cut from opening packaging). |
| 114 | "…or Human Factors Engineering (HFE) Report (see section IV.C.)" | Add: "Therefore the analysis may be submitted under an IND or BLA/NDA." | Text altered to identify which HF submission type is applicable to which application pathway to prevent the submission of unnecessary information. |
| 126 | "User task description and categorization (e.g., critical)" | Reference relevant guidance in footnote 21 that describes how to identify critical tasks. Further, it would be helpful to provide examples of critical and non-critical tasks. | As written, it is not clear if this is specifically referring to critical tasks. Inclusion of the recommended information would add clarity and consistency in approach. |
| 128 & 130 | "mitigation strategies" | The term "mitigation strategy" is used without reference to risk management. Renaming this term "risk control mitigation" would ensure this activity is linked to the risk mitigation process. | As identified within the Combination Product HF Draft Guidance: "Consistent with a risk-based design and development paradigm, the foundation for HF study designs, testing and evaluation should be a use-related risk analysis of a combination product." As part of this |

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| | | | process, the level of risk is used to drive the need for risk mitigation. |
| 132-141 | • "Description of intended product users, uses, use environments, and training (if applicable)"<br>• "Graphical depiction and written description of product user interface (see Appendix C for example)"<br>• "Summary of known use problems with previous or similar products"<br>• "Summary of preliminary analysis and evaluations, including formative evaluation" | These bullet points should be listed under a "1. Background" Heading, similar to how these elements are listed in Section IV.B and IV.C. The remaining bullets can be listed under a "Risk Analysis" heading. | This organizes the submission more clearly and mimics the structure of the other submission types detailed in the Draft Guidance. |
| 138 | "Summary of known use problems with previous or similar products" | "Summary of known use problems with previous **and/**or similar products" | In some instances where there are previous products available, it may also be beneficial to review known use problems with similar products. |
| 146-147 | "A sponsor can employ the use-related risk analysis to identify the need for risk mitigation strategies and to design an HF validation study..." | "**If a product includes a device constituent part**, a sponsor can employ the use-related risk analysis to identify the need for risk mitigation strategies and to design an HF validation study..." | To reduce unnecessary reviews for FDA, it would be helpful to provide in the Draft Guidance the conditions when a use-related risk analysis is required (e.g., when the product is a combination product). In the latter situation, it would be helpful to include examples from past Agency experience where the submission of analyses is warranted. Otherwise, sponsors may have to assume based on this Draft Guidance that every drug product in development would require a submission of a use-related risk analysis and threshold analysis to FDA. Coupled |

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| | | | with the fact that the timeframe of review for analyses is unspecified, this presents a challenge for sponsors in planning development activities. |
| 149 | "…sponsor determines that an HF validation study is not needed…" | Reference HF/UE Guidance, which describes this process (e.g., include a footnote giving an example of instances where a validation study would not be needed). | The requirement is not clear as currently written. Referencing the approach within existing guidance would promote consistency. |
| 166-168 | "...sponsors should provide a Word version to facilitate the exchange of labeling comments and revisions between the sponsor and FDA." | For labeling review comments regarding layout and format, it would be very helpful if FDA is amenable to commenting directly on the intended commercial printed layout version (i.e., layout PDF). | We understand that review of the Word version aligns with how other types of drug labeling are reviewed. However, for an IFU where the layout and form factor are just as important as the content, it's often difficult to understand the rationale for FDA's comments when it's described in the Word file. |
| 167 | "...in addition to an intended commercial printed layout version..." | "...in addition to an intended commercial printed layout version **or a representation of the expected presentation**…" | As discussed in our comments above, the intended commercial presentation may not be finalized; only content relevant to the user interface should be required. |
| 173-177 | "Summary of preliminary analyses… | Format this text to match the formatting of lines 244-251. Alternatively, to avoid duplicating text, refer to the relevant protocol section. | To ensure consistency between the HF validation protocol and report within this Draft Guidance. |
| 175 | "(e.g., device constituent part design change, labeling changes)" | Remove this entire parenthetical phrase. | The term "user interface" is defined elsewhere in other guidance documents; examples may only confuse the reader as to what's expected. For example, by specifically calling out "device constituent design change, labeling change," the |

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| | | | reader may think that all such changes must be described, rather than just those related to the user interface. |
| 177, 250-251 | Update the product user interface and use-related risk analysis | Improve consistency for contents related to summary of preliminary analyses and evaluation with existing HF/UE Guidance and remove the requirement to include changes of use-related risk analysis resulting from preliminary analyses. Reference Appendix A, Section 6 in HF/UE Guidance. | The wording here indicates the sponsor needs to include changes of use-related risk analysis resulting from preliminary analysis in the protocol background and HF study report; however, no further context is provided on the expectation. Existing HF/UE Guidance (see Appendix A, Section 6) does not include changes to use related risk assessment as part of the summary of preliminary analyses and evaluation. |
| 180 | “Analysis of hazards and risks associated with use of the product in a use-related risk analysis” | Add: "Refer to lines 117 to 130 for content." | The same content that would be expected in a stand-alone risk analysis submission should be the same as the risk analysis that accompanies the HF validation study protocol. |
| 182 | “HF validation testing details” | Add the following note after "details": "Note that the testing details listed below may be separately prepared in a defined protocol (e.g., in the case where a HF testing contractor is used) with the Background and Analysis of hazards provided separately by the sponsor." | This allows for an alternative approach in the case where a contractor conducts the study. |
| 186<br><br><br>264 | (Protocol): “Type of testing (simulated use vs. actual use)”<br><br>(Report): “Rationale for test type selected (simulated-use or actual use)” | Add the “Rationale for test type selected” within the Protocol requirements | If required as part of the review of the validation program, review of the rationale for the type of test should be completed with the protocol, which should be reflected in the Draft Guidance |

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| | | | text. This will ensure any disagreement with this rationale can be discussed prior to completing the study. |
| FN 21 & FN 28 | "See Combination Products Human Factors Draft Guidance), available at…" | (1) Remove extraneous ")" after "Guidance" and (2) correct the name of the guidance document to "Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development" | To ensure consistency and avoid confusion. |
| 210-285 | "Human Factors Validation Study Report…" | While the content for this report is similar to that within the HF/UE Guidance, it does differ in terms of structure and layout. In order to keep this consistent, we propose removing this information and instead referring to Appendix A of the HF/UE Guidance. | Many companies produce both combination and medical device products under the same procedures, so by keeping the requirements across these consistent, it ensures efficient and consistent generation of these reports. |
| FN 25 | "If the HFE process identifies no use errors or problems that could result in harm…" | "If the HFE process identifies ~~no~~ use errors or problems that could result in harm…" | Typographical error. |
| 222-226 | "If additional mitigation measures are needed, the study report should include a description of the additional mitigation measures and justify whether additional validation testing is not warranted. However, if additional validation testing is needed, the results should be submitted within the report." | "If additional mitigation measures are needed, the study report should include a description of the additional mitigation measures and justify whether additional validation testing is not warranted. However, if additional validation testing is needed, the results should be submitted within ~~the report~~ **a separate HF Validation submission**." | With the last sentence, it's not clear if the current validation report must be kept open until re-validation is complete. Re-validation would typically be a separate study and have its own protocol and report. |
| FN 26 | "If previously submitted, cross-reference the prior submission and include the eCTD sequence number and date of | "If previously submitted, cross-reference the prior submission and include the eCTD sequence number and | Analyses, protocols, and reports are typically standalone, version-controlled quality documents created outside of |

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| | submission. Sponsors should not resubmit the electronic files when referencing that document." | date of submission **in the submission cover letter and/or the appropriate eCTD section to facilitate review**. Sponsors should not resubmit the electronic files when referencing that document." | regulatory submissions. Therefore, it's not feasible to reference a submission sequence number within a study report. Instead, the validation report could reference the document number of another document (e.g., protocol number). It could then be explained in the cover letter or the submission sections where the cross-referenced information is located. |
| 253-255 | "Reference to previous HF validation study protocol submission…that occurred during the study." | Add, "if applicable." | To account for situation where a HF validation study protocol was not required. |
| 260 | “HF validation testing details” | Add the following note after "details": "Items in this section may be provided separately in a defined stand-alone report (e.g., in the case where a HF testing contractor is used) with the sponsor providing the Elements 1, 2, and 3, separately in the submission." | To allow for an alternative approach in the case where a contractor conducts the study. |
| 260-287 | “HF validation testing details…” | Allow cross referencing of sections from the Human Factors Validation Report to the Human Factors Protocol. | The content of the Human Factors Validation Protocol and Human Factors Validation Report requested in the Draft Guidance contains several duplicate sections related to study background, including summaries of known use problems and preliminary analyses. To avoid duplication of this information, which could result in inconsistencies and reduce the efficiency of the generation and review of these documents, we |

| Line Reference | Draft Guidance Text | Proposed Revision/Comment | Rationale |
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| | | | suggest the ability for the Report to cross reference sections within the Protocol. |
| 268 | "…and how it will correspond to real-world…" | Replace "will correspond" with either "would correspond" or "corresponded" | As this is a report, the description should be in the past tense. |
| 285 | "…discussion of risk mitigation strategies" | "…discussion of risk mitigation strategies **that were implemented**" | To clarify that this is a description of strategies that have already been implemented and not ones that are intended to be implemented in the future. |
| 291 | "Threshold analyses generally are utilized in comparing two drug products." | "Threshold analyses generally are utilized in comparing **the user interfaces of** two drug**-device combination** products." | To clarify the scope and utility of a threshold analysis. |
| 294-304 | "1. Labeling comparison… 2. Comparative task analysis… 3. Physical comparison of the device constituent parts…" | Switch the order of items 1 and 3 | The user tasks and labeling should be analyzed in the context of the physical device, and therefore should be compared first. |
| 295 | "..(a side-by-side, line-by-line comparison between the proposed product and the product it references that includes the full prescribing information, instructions for use, container labels and carton labeling, and descriptions of the products)" | "…(a side-by-side, line-by-line comparison between the proposed product and the product it references that includes the full prescribing information, instructions for use, container labels and carton labeling, and descriptions of the products**, as related to dosage and administration and instructions associated with safe and effective use of the product**)" | There may be many differences in the PI and a line-by-line comparison between the labeling of the two products would generate very little value. Also, a biosimilar combination product may use an IFU version that is validated for its device platform. It may not be appropriate and could create risk to users to apply the reference product labeling to a biosimilar or interchangeable combination product because the originator's IFU wasn't designed for the follow-on product's device. |

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| 297 | "…descriptions of the products" | Delete this requirement (in this section) and move to the physical comparison section (line 302). | This phrase is in the labeling comparison section; description of products should be discussed within the physical comparison section. |
| 299-300 | "Comparative task analysis (a comparative task analysis of the proposed product and the product it references)" | "Comparative task analysis (~~a comparative task analysis~~ **an analysis comparing the tasks of use** of the proposed product and the product it references)" | To provide further definition as a comparative task analysis is not explicitly defined. |
| FN 30 | "FDA recommends that sponsors analyze the differences with the goal of characterizing the potential for use error." | "FDA recommends that sponsors analyze the differences with the goal of characterizing the ~~potential for use error.~~ **use-related risks**." | The foundation for HF study designs, testing and evaluation should be a use-related risk analysis of a combination product and this should also be applicable to these types of assessments. |
| FN 30 | "See the [AAMI/ANSI] HE75:2009…" | Please specify which section(s) of the document the reader should review. | This reference document is large and identifying the relevant section would allow sponsors to focus on the relevant information. |
| 302-304 | "Physical comparison of the device constituent part(s) (e.g., **examine, through a visual or tactile examination, the physical features of the product** that it plans to reference and compare them to those of the proposed product) (emphasis added)" | Please clarify to what extent the physical features should be examined. An example showing the level of detail would be very useful. | A simple visual comparison can be conducted relatively quickly and easily, whereas a detailed characterization of geometry and operational forces may be difficult, especially given that the reference product specifications are not typically available. |
| 391 | "Observations of task performance…" | Format this text to match the formatting of lines 280-281. Alternatively, to avoid duplicating text refer to the relevant protocol section. | To ensure consistency between the HF validation protocol and report within this Draft Guidance. |
| 405-407 | "In addition, sponsors should submit HF validation study results reports or | "In addition, sponsors should submit HF validation study results reports **(i.e.,** | Text altered to identify which HF submission type is applicable to which |

| Line Reference | Draft Guidance Text | Proposed Revision/Comment | Rationale |
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| | comparative use HF study results reports in their application for FDA review (i.e., NDA, BLA, or ANDA)." | **NDA, BLA)** or comparative use HF study results reports **(ANDA)** in their application for FDA review ~~(i.e., NDA, BLA, or ANDA)~~." | application pathway, in order to prevent the submission of unnecessary information. |
| 464-481 | "The eCTD leaf title of the document should be clear, concise, and indicative of the content. Examples include…" | The examples provided in the Draft Guidance are related to requests and cover letters (i.e., Module 1.2). It would be helpful to have standard leaf titles for the protocol/report/analyses themselves and the appropriate way to title if there is more than one version of the document (e.g., from re-validation). | To facilitate review and ease of identifying the documents. |
| 506-509 | "...or a lengthy or complex response to an FDA question, or amends original submission materials with new information for any reason, FDA ordinarily will not respond to the original questions and will consider the original protocol submission withdrawn." | FDA should provide a means to address clarifying questions without the withdrawal of the entire protocol and additional 60-day review as this text suggests. | This would allow for questions not related to the methodology or results of the study to be addressed, without adding a further full review to the overall number of HF submissions received by FDA. |
| 591 | "Close calls: Instances in which a user almost makes a use error that could result in harm, but the user takes an action to "recover" and prevent the use error from occurring." | None | This definition aligns with the IEC and AAMI definitions of "Close Call," but not with the Combination Product HF Draft Guidance, which defines a "Close Call" as including the commission of a use error, but that the user self corrects. As identified within the general comments, a single glossary of FDA HF terms is required to ensure consistency. |
| 649 | "Residual use-related risks: The risks that remain after risk control measures have been taken." | "Residual use-related risks: The **use-related** risks that remain after risk control measures have been taken." | Definition should be specific to use-related risks. |

| Line Reference | Draft Guidance Text | Proposed Revision/Comment | Rationale |
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| 656 | "Task Analyses" | Replace with "Task **Analysis**" | The singular form should be used in the definition. |
| 669-671 | "Use error: A user action, or lack of action, that was different from that expected by the manufacturer and that caused an outcome that (1) was different from the result expected by the user, (2) was not caused solely by product failure, and (3) did or could result in harm" | Please harmonize this definition of "use error" with the definition given in IEC62366-1-2015 Medical devices – Part 1: Application of usability engineering to medical devices. | The IEC 62366-1-2015 definition is as follows: "USER action or lack of USER action while using the MEDICAL DEVICE that leads to a different result than that **intended** by the MANUFACTURER or expected by the USER." |
| 753-761 | Hypothetical example of HF validation data | Please include the results and analysis of the final validation study as well as the "failed" validation study. Please also provide an additional example where use errors or difficulties were observed, but residual risk was acceptable. | This example is of a validation study failure that leads to redesign and then another validation study. However, the results of the final validation study are not shown in this example. This could therefore be misleading. |