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FDA-2015-D-4848

VIA ELECTRONIC SUBMISSION

May 2, 2016

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

Re: Docket No. FDA-2015-D-4848: Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development

Dear Sir or Madam:

The Combination Products Coalition ("CPC")[1] welcomes the opportunity to offer comments on FDA's "Draft Guidance for Industry and Staff: Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development" ("Draft Guidance"). We believe the Draft Guidance is a positive step forward in clarifying FDA's expectations regarding the role of human factors ("HF") testing in combination product development, which facilitates development of innovative therapies that will benefit patients.

Overall, the CPC agrees with many of the recommendations in the Draft Guidance, but believes revisions are needed to: (1) resolve inconsistencies between the Draft Guidance and other FDA guidance documents, (2) better define the relationship between HF testing and clinical studies, (3) clarify expectations with respect to revalidation of post-HF validation changes, and (4) clarify when HF testing is required for combination products and the scope of such testing. We also include minor editorial suggestions in Appendix A.

[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.

I. Inconsistencies between the Draft Guidance and Existing HF Standards and Guidance

We believe FDA's goal in issuing the Draft Guidance was to foster consistency in the application of HF across Agency Centers. Thus, the Draft Guidance should remain consistent with established FDA policies in other guidance documents, address nuances that would exist with combination products and advance a common lexicon of terms for HF evaluations. To fulfill these objectives, it is important that FDA: (1) incorporate recommendations from FDA's "Guidance for Industry and FDA Staff: Applying Human Factors and Usability Engineering to Medical Devices" ("CDRH HF Guidance") into the Draft Guidance, except where necessary to address combination product-specific nuances; (2) use the same terminology in the Draft Guidance and other FDA HF guidance documents; and (3) ensure terms are defined consistently across its guidance documents. To that end, we recommend that FDA incorporate the following changes:

1. FDA should add language to the "Introduction" section of the Draft Guidance explaining that the Draft Guidance is intended to explain how to apply the concepts addressed in previously issued FDA guidance documents to combination products. This language should clearly explain that the Draft Guidance is not intended to contradict or replace the CDRH HF Guidance, the "List of Highest Priority Devices for Human Factors Review: Draft Guidance for Industry and Food and Drug Administration Staff" ("High Priority Review Draft Guidance") or the HF issues addressed in FDA's "Safety Considerations for Product Design to Minimize Medication Errors: Guidance for Industry" ("Medication Error Guidance"). This language should also indicate that if a specific HF issue is not addressed in the Draft Guidance, but is addressed in other guidance documents, such as the CDRH HF Guidance,[2] sponsors should refer to the recommendations in those other guidance documents. Further, to the extent FDA intends for a provision of the Draft Guidance to supersede previous guidance,[3] FDA should expressly state that in the Draft Guidance.

2. We recommend FDA update the Draft Guidance to use the terminology already established and defined in the CDRH HF Guidance, and only use new terminology where necessary. Specifically, we recommend that FDA replace the following defined terms used in the Draft Guidance with the corresponding terms from the CDRH HF Guidance, as described in the chart below.

[2] For example, a few categories of information that are omitted in the Draft Guidance, but are found in the CDRH HF Guidance, include information regarding sample size for HF Validation Testing, a more complete discussion of residual risk and information regarding the HFE/UE report format.

[3] For example, if FDA intends for the Draft Guidance to expressly supersede the discussion of generally applicable HF issues in the product specific "Draft Guidance for Industry – Rheumatoid Arthritis: Developing Drug Products for Treatment," we recommend that FDA clearly state that in this Draft Guidance.

Term from Draft Guidance	**Corresponding Term in CDRH HF Guidance**
HF Formative Study	Formative evaluation
HF Validation Study	Human factors validation testing
HF Study	Human factors testing[4]

3. In conjunction with the change suggested directly above, we recommend FDA delete the definitions of "HF Study," "HF Formative Study" and "HF Validation Study" on lines 112-39 of the Draft Guidance and instead defer to the definitions of these terms in the CDRH HF Guidance.[5] Further, for reasons detailed in Section II below, we recommend that FDA not use the terms "study" or "studies" when referring to formative evaluations or HF validation testing, and instead use the terms "test," "tests" or "testing."

4. FDA should address the inconsistency between how the Draft Guidance and CDRH HF Guidance define the term "critical tasks." The Draft Guidance defines "critical tasks" as those "user tasks that if performed incorrectly or not performed at all, would or could cause harm to the patient or user, where *harm* is defined to include compromised medical care (emphasis added)." The CDRH HF Guidance defines the term to mean "user task[s] which, if performed incorrectly or not performed at all, would or could cause *serious harm* to the patient or user, where harm is defined to include compromised medical care (emphasis added)." We propose that the Draft Guidance be amended to defer to the definition in the CDRH HF Guidance. In addition to ensuring consistency, this revision accounts for the fact that it is not necessary for use-related risk analysis to identify every task that could theoretically cause any harm, especially where the risk is extremely low and the potential harm is not serious, as this would slow down the development process, delaying patient access to new products.

   Although we are asking FDA to defer to the CDRH HF Guidance's definition of "critical tasks," we do believe that the Draft Guidance could clarify the scope of "compromised medical care" included in the definition of "harm" by explaining that in the context of combination products, examples of compromised medical care include overdosing and under dosing.[6]

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[4] Although not a defined term, the CDRH HF Guidance uses the term "human factors testing," whereas the Draft Guidance uses the term "human factors studies." As discussed in greater detail below, we are concerned that referring to HF testing as "studies" inappropriately implies that HF testing constitutes a clinical study.

[5] While the CDRH HF Guidance does not expressly define "HF testing," it does include specific definitions for "formative evaluation," "HF engineering," and "HF validation testing," and describes HF testing throughout. However, to the extent FDA believes that HF testing should be defined in the Draft Guidance, we suggest FDA simply define HF testing as "the performance of formative evaluations and human factors validation testing, as those terms are defined in the CDRH HF Guidance."

[6] In addition, we recommend that FDA revise the following listed critical task example in line 194: "The user being able to safely dispose of a used syringe." We recommend this example be deleted or at least a footnote be added that would read: "This may not be a critical task if the sponsor determines that steps a user would follow

II. Relationship between HF Testing and Clinical Studies

The CPC is concerned that the Draft Guidance could be misinterpreted to suggest that: (1) HF testing constitutes a clinical study and data derived from HF testing may be clinical data, and (2) combination products will need to be evaluated as part of clinical studies prior to approval. Our comments in this section describe why HF tests are not generally clinical studies, and how the Draft Guidance should be amended to clarify this distinction. This section also explains why clinical studies are not necessary to evaluate the safety and effectiveness of all combination products and outlines our proposal for the sequencing of HF testing and clinical studies (when clinical studies may be required), as well as sequencing within HF testing itself. Finally, our comments in this section propose certain changes to the definition of HF Actual-Use Validation.

A. Distinguishing HF Testing from Clinical Studies and HF Testing Data from Clinical Data

We ask that FDA make certain changes to the Draft Guidance so that it is clear that HF tests are not generally clinical studies, and that data from HF testing are not considered clinical data. Although HF testing may involve humans, these tests are not "clinical studies" as that term is usually understood. As FDA states in 21 CFR § 314.126 "[t]he purpose of conducting clinical [studies] of a drug is to distinguish the effect of a drug from other influences." On the other hand, HF testing is intended to "assess the adequacy of the combination product user interface design to eliminate or mitigate potential use-related hazards."[7] In other words, clinical studies focus on how the combination product affects the patient, whereas HF testing focuses on how the patient interacts with the combination product. Further, the primary purpose of a clinical study is to evaluate clinical endpoints through the collection of objective clinical data. Conversely, HF testing does not evaluate clinical endpoints and instead focuses on the collection of objective and subjective observational data. Additionally, HF tests have not historically been treated as clinical studies, and referring to them as clinical studies now could have undesirable consequences, such as subjecting NDA/BLA supplements to extended review times and triggering user fees, which could hinder innovation, and ultimately, patient care.

To clarify the differences between HF testing and clinical studies, and between HF data and clinical data, we recommend that FDA make the following additional changes:

1. Revise the title of the Draft Guidance to read: "**Applying** Human Factors **to** ~~Studies and Related Clinical Study Considerations in~~ Combination Product Design and Development."

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independent of this particular combination product (e.g., aseptic technique or standard disposal practices) are not critical."

[7] Draft Guidance (lines 112-14).

2. Revise the sentence in lines 22-23 of the Draft Guidance to read: "[T]he guidance describes how HF ~~studies~~ **testing** relate**s** to ~~other~~ clinical studies." Similarly, revise line 65 to read: "What is the role of HF ~~studies~~ **testing** as compared to ~~other types of~~ clinical studies?"

3. Revise the definition of "Major Clinical Study (or Major Clinical Trial)" as follows: "~~*Major*~~***Pivotal*** *Clinical Study (or* ~~*Major*~~***Pivotal*** *Clinical Trial)*: As opposed to **HF testing**~~a HF study~~, a ~~major~~**pivotal** clinical study is a large~~r~~ scale clinical study that ~~occurs during a later phase of combination product development. Clinical studies~~ provide**s** the primary support for the safety and effectiveness of a product for a proposed indication (e.g., adequate and well-controlled studies)**, whereas HF testing assesses the adequacy of the combination product user interface design to eliminate or mitigate potential use-related hazards**. **HF tests generally are not clinical studies.**"

Further, to avoid confusion about whether NDA or BLA supplements that contain HF data are clinical supplements that are subject to additional review times and user fees, we ask that FDA revise the Draft Guidance to state that HF testing data should not be considered clinical data. To accomplish this, we ask that FDA update Footnote 7 of the Draft Guidance by revising the last sentence as follows: "…~~As applicable, FDA will determine whether a HF study would meet these criteria.~~ **However, HF data should not be considered clinical data**." Because HF testing data do not fit within the scope of "clinical data" established by FDA's "Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees" ("User Fee Guidance"),[8] it is unnecessary for the Draft Guidance to defer to the User Fee Guidance. Further, our suggested revision is consistent with FDA's statement in the Medication Error Guidance, which provides that data from HF testing are not sufficient to demonstrate the safety and effectiveness of a combination product. This also is consistent with FDA's position that data from bioavailability and bioequivalence ("BE/BA") studies are not considered clinical data for the purposes of assessing user fees; data collected from HF testing are even "less clinical" than BE/BA study data as they do not include administration or actual use of the test article in its entirety (e.g., medication is not administered).

B. Sequence of HF Testing and Clinical Studies and Other Timing Considerations

In addition to our concern about HF tests being construed as clinical studies, we are also concerned about how the Draft Guidance characterizes the sequence of HF testing relative to clinical studies. While we acknowledge that the appropriate sequence will be a product-specific determination, we believe the Draft Guidance should include a more defined position. For example, the Draft Guidance notes that HF Validation Testing should be conducted before conducting a pivotal clinical study, but also notes that in some cases, it may be appropriate to

[8] For the purposes of assessing user fees, the User Fee Guidance defines "clinical data" to encompass "a broad range of studies that are purported to be adequate and well-controlled investigations submitted in support of approval" (e.g., adequate and well-controlled trials for safety or effectiveness, and reports of comparative activity, immunogenicity of efficacy where those reports are necessary to support a claim of comparable clinical effect).

conduct HF testing in parallel or following the completion of a pivotal clinical study. The absence of a clearly defined position gives FDA reviewers significant leeway to dictate when HF testing should occur in relation to clinical studies, which could potentially be disruptive to product development. To offer clarity and consistency to sponsors, we recommend that FDA simply state that the sequencing of HF testing and clinical studies should be determined based on the sponsor's risk assessment. FDA will have the opportunity to evaluate the sponsor's risk assessment as part of its IND or IDE review process.

Also regarding timing, the Draft Guidance should state explicitly what review and response timing can be expected for HF protocols reviewed within an investigational application; our recommendation would be that responses can be expected within 30 days. Timely review is important to ensuring efficient development of innovative products that provide patient benefit. We would prefer that the Agency review the HF information via a defined protocol review, rather than via an IND information amendment. FDA has routinely requested three to four months for its reviews submitted in an IND information amendment, and resolution of FDA's feedback when received can take additional months. On the other hand, responses to IND applications with study protocols have more typically been received within 30 days.

To expedite the FDA feedback process, we also recommend that FDA add the following language in line 552 (before the sentence that starts with "Also, during…"): "It is not expected that the HF information submitted for feedback will be in the detailed form that will eventually be submitted in the final application for product approval." In addition, lines 552-54 should be revised to read: "Also, during Agency review of draft HF Validation ~~study~~**Testing** protocols that include product labeling (e.g., instructions for use), FDA intends to provide preliminary comments on the user interface labels and labeling being **submitted, as well as the data supporting the user interface labels and labeling obtained from Formative evaluations**."

C. Defining Actual-Use Validation

Finally, turning to FDA's definition of "HF Actual-Use Validation," we believe that additional clarity is needed. The Draft Guidance states that HF Actual-Use Validation testing "either (1) use[s] the final finished combination product (including the drug, not a placebo) in a simulated use setting or (2) use[s] the final finished combination product in a real (not simulated) environment of use." We do not believe that this definition clearly captures the difference between Simulated-Use and Actual-Use Validation. Generally, Simulated-Use Validation is the use of the product (which can include the actual drug or a nonreactive surrogate) in a simulated use setting. For example, when using the term simulated use with respect to injector system combination products, the term is intended to mean use of an injection pad. If a sponsor does an actual injection into a human subject (regardless of whether the actual drug or a nonreactive surrogate is being used) in a real or simulated use setting, that is Actual-Use Validation.

While Actual-Use Validation may be required for combination products in cases where Formative evaluations have shown that performing the actual delivery can affect use of the product (e.g., pain of the injection impacts the user's ability to properly inject), we believe that Actual-Use Validation should rarely be needed. Accordingly, we are supportive of FDA's acknowledgement that for most combination products, HF Simulated-Use Validation is sufficient to assess the adequacy of the user interface design (as opposed to requiring HF Actual-Use

Validation). We ask that FDA take this one step further, however, and include language in the Draft Guidance stating that HF is best assessed in HF Validation Testing, and in most cases, usability assessments should not be performed in clinical studies. Obtaining reliable usability information in clinical studies designed to evaluate other endpoints is challenging because clinical study participants often have more extensive training than representative users; as such, collecting HF data in controlled clinical studies may not be sufficiently representative of the end use scenario. Also, clinical study design to assess usability must allow for use errors to occur. Such use errors may confound clinical data or present ethics issues. Therefore, HF assessment should not be part of clinical studies.

III. Post-Validation Changes

For post-validation changes, our concerns with the Draft Guidance relate to its suggestions regarding: (1) the scope of post-validation changes that require revalidation, and (2) accommodating FDA-suggested labeling improvements late in the review cycle after HF testing has been successfully conducted. We detail each of these below.

A. Scope of Post Validation Changes that Can Be Conducted Without Validation

The CPC agrees with FDA that HF Validation Testing would ideally be conducted on combination products and labeling that are very close to the to-be-marketed versions. However, there are frequently instances where changes will need to be made after the HF summative validation is completed. The need for post-validation changes often arises for the following reasons:

- Regulatory submissions for combination products regulated as drugs are typically prepared months or years before a product is launched and changes may be made in drug-related labeling between the investigational stage and commercial launch as part of a regulatory review.
- At the time of HF Validation Testing, sponsors only may have run preliminary manufacturing batches, which are representative of the commercial product, but may be manufactured on different manufacturing lines.
- Minor design changes are implemented to improve patient convenience or other factors that are unlikely to have a significant impact on a product's safety or effectiveness.

If HF revalidation is frequently required for changes, it can delay the approval of combination products for several months or longer, which keeps beneficial products out of the hands of patients. Accordingly, it is imperative to consider: (1) what the likely effects of a change would be, and (2) whether it is likely that these effects would materially alter the risk-benefit analysis underlying approval of a combination product. Therefore, sponsors should be able to make risk-based determinations on whether changes to the validated combination product or its labels and labeling warrant any additional HF testing.

Examples of changes that would generally not require revalidation include: (1) self-administered combination products where changes to labeling do not affect use instructions (and hence are unlikely to affect product use); (2) basic editorial changes that are unlikely to affect

use (e.g., changing from "manufactured for" to "distributed by" and adding a branding logo or manufacturer's name to packaging, labels or labeling); and (3) changes to labeling or design that would not affect approvability because even assuming the most pronounced effects, the benefits would exceed the risk (which might occur, e.g., for a product for an unmet medical need or with a substantial margin of effectiveness over controls). In these latter cases, to the extent testing might be desirable, it would be reasonably included as a Phase IV commitment, but it should not prevent the approval of a product that has sufficient data to support safety and effectiveness even with some margin of uncertainty with respect to labeling or design changes. Conversely, where changes could have a significant impact based on risk analysis, such that the change could affect the approvability of the combination product, revalidation prior to approval might be necessary.

To address the need for a risk-based framework in assessing the need to revalidate HF prior to approval, we propose the following changes:

1. FDA should clarify that not all changes to the Final Finished Combination Product (which includes the proposed packaging, labels and labeling) would require revalidation to the extent that the user does not interface with the changed aspect of the Final Finished Combination Product when performing critical tasks (e.g., changes to drug labeling that are not critical (per risk assessment) to the safe and effective use of the combination product by the end user), or would not otherwise be significant enough to change the risk-benefit analysis in favor of delaying approval. To accomplish this, we ask that FDA:

    a. Revise lines 546-47 as follows: "~~Intend-to-market l~~**Labels** and labeling (including instructions for use if any are proposed) that will be tested in the HF Validation ~~study~~**Testing**."

    b. Revise the "Final Finished Combination Product" definition to read: "The final finished combination product ~~is the product intended for market and submitted in the marketing application~~ **includes initial production units, lots, or batches, or their equivalents, manufactured using the same methods and procedures expected to be used for ongoing production. The studied samples (1) must be representative in use and risk to those of the expected commercial product, or (2) sufficiently similar to to-be-marketed product presentations such that uncertainties about performance effects (if any) are unlikely to make the product non-approvable.** This term applies to the combined final device, drug, and/or biological product configuration including all product user interfaces (e.g., proposed packaging, labels and labeling, including **required** training programs)."

2. FDA should allow sponsors to propose (and obtain agreement from) the Agency that certain changes to the product's physical user interface or critical packaging, labels or labeling do not require revalidation. These would be changes to aspects of the product that the sponsor could demonstrate are not critical to approvability or that have been sufficiently validated in prior HF testing (this request could potentially be

made as part of the HF Validation report or the accompanying risk analysis that is submitted to FDA prior to validation testing, or after testing is completed).

3. FDA should provide additional examples of changes that may not require validation.[9] In addition, we ask that FDA promote the use of risk analysis by sponsors to determine if a post-validation design change requires HF testing. FDA could do this by revising the sentence on lines 503-05 as follows: "**Applicants should determine, via their risk analysis procedures, whether** ~~However,~~design changes made after HF Validation that relate to identified critical tasks or may result in new use-related errors or hazards that could lead to harm should have new HF Validation ~~study~~ assessments."

4. FDA should amend lines 522-25 to read: "~~When~~ **If after** making a design change to a combination product, **applicants are unclear what** ~~FDA encourages applicants to expeditiously identify the change plans and to discuss with the Agency the~~ types of HF **testing,** ~~and other~~ clinical **studies** or non-clinical studies ~~that~~ may be applicable**, FDA encourages applicants to review the changes with the Agency** before ~~the applicant's approval of~~ **proceeding with additional testing or studies to validate** the design change**s**." The revisions in this sentence are requested as design changes are typical and frequent in the development process, and there is already a process in place to manage these changes. The request for a summary of changes made to the device during device development goes beyond what is required by FDA in a device submission. Development activities during the iterative design process need not be reviewed as long as the final device design is adequately supported by verification and validation activities, including HF testing.

B. Accommodating Late-Cycle or Post-Validation Labeling Change Requests from FDA

It is not uncommon for sponsors to receive requests from FDA late in the review cycle or after HF testing has been conducted requesting that sponsors change their labeling even though the validation suggests that the labeling is sufficiently effective to guide use of the product. These kinds of post-hoc (after validation) requests to make changes, particularly late in the review cycle, can be highly disruptive and lead to delays in approval that keep safe and effective products from reaching patients for months or longer. Therefore, we ask that FDA:

1. Clarify its process for determining whether the final user interface labeling for a product should differ from labeling that was used in the HF Validation Testing. We believe that the content and format of labels and labeling should be reviewed as part of the HF protocol and draft Instructions For Use ("IFU") reviews, with sponsors ideally addressing any FDA feedback prior to conducting HF testing.

[9] We recognize that the Draft Guidance states that "[s]ome modifications to a product's internal design or to some of its external features may not need validation in [HF testing] (e.g., a change in a material that does not affect user interface)." However, we ask that further clarity be provided through examples.

2. Revise the Draft Guidance to encourage sponsors to engage in discussions with FDA regarding labeling prior to conducting HF Validation Testing.

3. Agree not to require changes to validated labeling that will impact a critical task already addressed in validated labeling unless: (1) FDA's request is based on results from a clinical trial involving the actual combination product, or other safety data or medication error data involving the actual combination product (i.e., not data involving similar products); and (2) FDA provides scientific rationale as to why the changes are needed to mitigate use-related risks. Further, we believe that in cases where FDA believes that labeling content or formatting changes may be beneficial based on postmarket or other experience with similar, but not identical products, these changes should only be suggested, and not required. To accomplish this, FDA should:

    a. Revise the language starting on line 569 be changed to read as follows:

    "During FDA review of labeling in a marketing application, FDA may determine that the final user interface labeling should differ from the HF Validated labeling. **In such a case, FDA will provide scientific rationale as to why the additional changes are needed to mitigate use-related risks.** This may occur, for example, based on the results of ~~the~~**a** ~~major~~ **pivotal** clinical trial, other safety data or medication error data, new nomenclature considerations, and labeling content and format requirements.[10] The labeling assessment also considers current postmarket experience with the combination product, ~~same or similar products,~~ which might indicate that modification of the instructions for use is appropriate to mitigate a risk. **If FDA believes changes are needed based on similar, but not identical products, these changes will only be suggested, not required.**"

    b. Add the following language to the paragraph ending on line 578:

    "**The need for additional HF Validation Testing will take into consideration the results of previous Formative evaluations and HF Validation Tests and Knowledge Task Studies before requiring additional testing. Further, sponsors may be granted the ability to conduct such HF Validation Testing post-approval, but prior to launch. FDA should work with the sponsor to identify any potential situations where additional HF Validation Testing may be needed prior to submission of the marketing application to ensure the application is complete and the testing supports the final labeling.**"

[10] We recommend that FDA provide references for the sources of these labeling content and format requirements.

IV. Clarifying When HF Testing is Required and the Scope of Such Testing

A final area where we believe clarification is necessary is in the Draft Guidance's discussion of situations in which FDA would generally require HF Validation Testing, and the scope of such required testing (including training considerations). This section also provides comments regarding how the Draft Guidance defines when an HF Validation Test will be considered failed.

A. Using a Risk-Based Approach to Determine the Need for HF Testing

Overall, we believe the Draft Guidance should encourage sponsors to take a risk-based approach in determining the need for HF Validation Testing, including conducting Formative evaluations to shape the design, risk analysis, and identification of hazards and potentially critical tasks, and to revisit risk analysis results after Formative evaluations. The Draft Guidance should also provide the option to (but not require) sponsors to seek advice from the Agency, via a formal meeting process, should there be any ambiguity about whether HF Validation Testing is required.[11]

In terms of Agency review of a sponsor's risk analysis, we believe that a summary of the risk analysis (rather than the full risk analysis itself, as recommended by the Draft Guidance) is most appropriate for submission to FDA in investigational applications. Risk analysis is a "tool" used by sponsors to evaluate and prioritize use related risks. Because it is a "tool," the process used by sponsors to conduct their risk analyses varies. For example, severity and occurrence ranking often varies. It would be burdensome for FDA to review the risk analysis line-by-line and interpret the information presented. Further, risk analysis is a living document that is updated throughout the lifecycle of the product in the sponsor's quality system. Submission of the risk analysis would also be impractical to maintain as current in the CTD Module 3. Accordingly, lines 533-36 should be revised to read: "**A summary of** ~~T~~**t**he risk analysis ~~itself~~ should be submitted in the investigational application for the combination product. If the applicant determines from the risk analysis that a HF ~~study~~**test** is not needed, the applicant should provide the **summary of the** use-related risk analysis along with the justification for this conclusion."

Further, we ask that FDA provide guidance to sponsors regarding when HF data can be leveraged for different products (e.g., products which utilize the same device component, but deliver different drugs, or products that undergo minor device design changes that do not impact usability).

B. Determining When HF Data is Required to Support Approval

According to the Draft Guidance, "generally human factors data should be submitted [for]: (1) products for use outside the health care environment or by laypersons (e.g., home-use products, products for self-administration by patients or lay-caregivers) and (2) combination

[11] Accordingly, before line 516, the following should be inserted: "If applicants determine there is ambiguity about whether additional HF testing is needed, they can (but are not required) to seek advice from FDA."

products having a device constituent part for which human factors data should be submitted." We ask that FDA provide further detail with respect to the scope of these two categories and clarify its expectations for combination products that fall outside of these two categories. Specifically:

1. The first category appears to be overly broad in that it could include OTC combination products, such as liquid medications with a dosing cup as they are used outside of the health care environment. However, we anticipate that this was not FDA's intent and therefore suggest FDA exclude these types of products from this first category.[12]

2. With respect to the second category, we assume that FDA is referring to the products described in the High Priority Review Draft Guidance. Therefore, we ask that FDA specifically reference that document in the Draft Guidance.

3. It is unclear whether FDA still expects HF testing (including HF Validation Testing) to be performed, but the corresponding data not be submitted, with respect to products falling outside of these two categories. Although we believe that FDA's intent is that HF testing does not need to be performed or submitted, we request that FDA clarify this.

We also believe that HF data should not always be required to be submitted for a pre-filled syringe ("PFS") with a staked needle for lay use. The Draft Guidance provides that HF Validation Testing would not be expected for a PFS with a staked needle for use by HCPs in an acute care setting (provided the design is commonly used and well understood). However, the Draft Guidance does not specify whether the same standard would apply for a PFS with a staked needle intended for lay use. We recommend that FDA apply the same standard, stating that if a sponsor is going from an already approved non-HCP administered injectable, HF Validation Testing would not be required to support bridging from a vial and syringe to a PFS where the product is intended for lay use. Like the HCPs, the lay users who would be using the PFS are those who have experience using syringes and needles and familiarity with these products. Products for which other types of design validation would be sufficient for evaluating usability, such as those intended to be used by medical professionals in a surgical setting such as surgeons, circulating/scrub nurses, should also be addressed in the Draft Guidance (i.e., clarifying that HF testing is not required for such products, if that is the case).

C. Scope of HF Testing

Turning to the scope of required HF testing, we have concerns about the Draft Guidance's recommendations with respect to training. Specifically:

1. FDA should state in the Draft Guidance that if a sponsor determines that training would be "nice to have," but is not necessary (e.g., because the risk the training

[12] This could be done through a statement noting: "This guidance does not apply to combination products containing nonprescription drugs marketed without an approved application (e.g., under a monograph)."

would mitigate is not a serious risk), then HF Validation Testing only needs to evaluate the user interface in the absence of training.

2. We ask that FDA adopt the position that if a sponsor commits to a training requirement in its labeling, then HF Validation Testing will not require an untrained user population for any user group that will be required to undergo training pursuant to the labeling. In accordance with ISO 14971, sponsors evaluate reasonable foreseeable misuse scenarios (including the possibility of untrained users) as part of the risk management process (e.g., through Formative evaluation). If sponsors adequately assess the risk of untrained use during this process, the inclusion of an untrained user group in HF Validation Testing is not warranted.

3. We do not believe it is reasonable to expect sponsors to ensure training will "routinely and consistently occur." Sponsors can, however, ensure that labeling clearly details the necessary training, who must be trained and who is responsible for training.

To address the CPC's concerns, we ask that FDA revise lines 269-74 as follows:

"~~On the other hand,~~ **[I]**f there are residual risks for which training may be appropriate, the next step is to consider whether there is an opportunity for training, and if so, whether ~~there is an expectation that training will routinely and consistently occur~~ **such training, when provided, is effective in addressing potential use-related errors**, before the first use of the combination product. **If training is deemed appropriate based on these factors, then realistic end use training should be provided in HF Validation Testing. If a sponsor includes a training requirement in its product's labeling, the sponsor will not be required to have an untrained user population for any user group that will be required to undergo training pursuant to the labeling. In addition, sponsors who include a training requirement in a product's labeling should clearly define the nature of the training, who must be trained and who is responsible for providing the training (e.g., a healthcare professional providing training to a patient).** ~~In cases where training would be appropriate but is not expected to routinely or consistently occur, the HF study should evaluate the user interface in the absence of training.~~"

D. Defining a "Failed" HF Validation Test

Finally, we recommend that FDA revise how the Draft Guidance defines a failed HF Validation Test. According to the Draft Guidance, an HF Validation Test will be considered failed if it "shows that additional measures are necessary to address the risk of failures that *are deemed clinically significant* (emphasis added)." We request that FDA revise this standard such that an HF Validation Test will be considered failed if it "shows that additional measures are necessary to address failures that *present serious risks*." We believe this change is important because although all clinically significant risks are serious risks, not all serious risks are necessarily clinically significant. For example, a serious risk may not be clinically significant if the user mitigates the risk (e.g., a user can mitigate a failed injection if he or she identifies the

failed injection and attempts to deliver the medication again). However, because there is no way to know if users will actually mitigate the risk, the focus should be on serious risks (regardless of whether they are clinically significant).

For additional clarification and alignment with the CDRH HF Guidance, we also recommend that the following language, adopted from the CDRH HF Guidance, be added at the end of the paragraph on line 392: "**HF Validation Testing results indicating that serious use errors persist are not acceptable in premarket submissions unless the results are analyzed well and the submission shows that further reduction of the errors' likelihood is not possible or practical and that the benefits of the combination product use outweigh the residual risks**."

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We hope our comments are helpful to the Agency as it develops its final guidance. If the CPC can help in any way, please do not hesitate to contact us.

Yours truly,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition

Appendix A: Additional Requested Revisions

Line/Section Reference	Proposed Revision/Reasoning
Lines 72-75	We recommend that the sentence be revised to read: "For medical devices, the use of human factors and usability engineering (e.g., applying the knowledge of human behavior, abilities, and limitations to the design of a medical device) plays a key role in maximizing the likelihood ~~that~~ **of safe and effective use of** the device **by the intended users** ~~will be safe and effective for use by the intended users,~~ for the intended uses, and for the intended use environments."
Line 179	In line with our comments in Section IV above, after the first full sentence in this line, we recommend inserting: "Previously unidentified risks observed during HF Formative evaluation should be included in the risk analysis and may serve to identify additional critical tasks."
Section III.B.2	We ask that FDA include language in this section to permit sponsors to use representative end users in testing where it is not reasonably possible for the sponsor to recruit actual users (e.g., in the case of rare diseases). We suggest the following language: "For certain distinct user groups (e.g. patients with a rare disease), it may be unreasonable for a sponsor to recruit actual end users to participate in HF testing. Under such circumstances, surrogate participants may be recruited to represent the intended end users provided the sponsor can justify that the surrogate participants and actual end users have closely matched characteristics."
Lines 221-24	We ask that FDA revise this sentence as follows: "Prior to performing a risk analysis, it is important to identify all intended users and use environments for the combination product. Intended users may be categorized into distinct user groups by their different characteristics (e.g., use responsibilities, tasks performed, age ranges, skills, ~~or~~ experience levels**, or by different drug indications, in the case of a drug-device combination product**)." An important characteristic of the user group could be the very disease state for which the product is indicated. For example, if a hand-held device has been approved for one indication, but is going to treat a new indication, a disease for which difficulty grasping is a characteristic of users with that disease, evaluating the validity of previous usability results may be warranted.
Lines 229-32	Because the appearance of a product is not as important as how the product operates and how the user interacts with the user interface, this sentence should be revised as follows: "Also, within the HCP user population there may be individuals that have experience with the use of similar products and individuals that do not (e.g., injector-experienced vs naïve) or that do or do not have experience with ~~similar appearing~~ products **that operate in similar ways** with different instructions for use or different hazards."
Line 312	After the sentence ending on this line, we recommend adding the following: "The evaluation design should provide for the identification of any unanticipated hazards or unexpected use behaviors that were not previously identified. In the event that a design problem is solved and the Formative evaluation verifies that the solution has mitigated a potential user risk, sponsors may conclude, in the

Line/Section Reference	Proposed Revision/Reasoning
	Formative evaluation report, that the design issue has been solved and the design is ready for HF Validation Testing (perhaps with a greater or different population of users), or that no summative testing is necessary, if applicable."
Lines 319-20	The sentence should be revised to read: "~~None of the~~ **I**~~i~~ndividual subjects **who participate** in ~~the~~ HF Formative ~~studies~~ **evaluations may participate in the HF Validation Test, but new participants should also be recruited** ~~should participate in the HF Validation studies~~ to avoid the potential for bias."
Lines 335-37	To improve clarity, this sentence should read: "The HF Simulated-Use Validation ~~study~~**Test** focuses on confirming that the design of the final finished combination product (i.e., after iterative prototype design changes) user interface adequately mitigates or eliminates the identified use-related risks **for critical tasks**."
Lines 346-48	We ask that FDA move this language ("The ~~study~~**test** design should provide for the identification of any unanticipated hazards or unexpected use behaviors that were not previously identified.") to the beginning of line 382 as this language should apply to both types of HF Validation Testing.
Lines 431-33	Because HF testing is not intended to be statistically powered, this sentence should be revised to read: "Certain types of Knowledge Task studies are also used in the development of non-prescription products. ~~Generally, these are quantitative studies that evaluate whether results are statistically significant~~ **Although the Knowledge Task studies used in the development of non-prescription products evaluate whether results are statistically significant, there are no expectations that statistically significant or powered studies be required for prescription combination products**." The CDRH HF Guidance supports this clarification, as it notes, "Human factors validation testing is primarily a qualitative rather than a quantitative exercise" (at p. 36).
Lines 475-78	We ask that this sentence be revised to read: "Even if factors such as indications for use, intended users, and use environment remain unchanged, based on the use-related risk analysis, **sponsors should determine whether differences are sufficiently obvious to obviate the need for** ~~an~~ HF Validation **Testing**~~study may be necessary~~ to ensure that HCPs can readily distinguish the new syringe from similar prefilled syringes containing different drugs."
Lines 583-84	The sentence should be revised to read: "As explained in preceding sections of this document, HF ~~studies~~ **testing** of a combination product ~~are~~ **is** conducted as part of the product ~~design controls~~ **development** process." This edit is appropriate because 21 CFR § 820.30 does not specifically require HF testing.
Appendix A	The Draft Guidance states that Appendix A identifies task failures generally, but the tables in Appendix A characterize the listed items as "Examples of *Critical Tasks* for Combination Products (emphasis added)." It does not appear to us that the task failures listed in Appendix A are in and of themselves "critical tasks." For these task failures to be considered "critical tasks," they would have to meet the definition discussed above (i.e., they would or could cause serious patient or user harm if performed incorrectly or not all as analyzed through a risk analysis). To address this, we request that FDA revise the table in Appendix A to read

Line/Section Reference	Proposed Revision/Reasoning
	"Examples of Product Use Tasks."
Appendix A: Table 1	The following language should be revised as these items are not described as tasks like the others on the list: • ~~Understand~~**Demonstrate** how to dose the product • ~~Understand~~**Demonstrate** how to administer the product • ~~Product differentiation~~**Selecting the correct product**
Appendix A: Table 2	The following language should be revised as these items are not described as tasks like the others on the list: • ~~Understand~~**Demonstrate** how to dose the product • ~~Understand~~**Demonstrate** how to administer the product