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May 4, 2016

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

Reference: FDA Draft Guidance for Industry: Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development; Docket No. FDA-2015-D-4848

Dear Sir/Madam:

PDA congratulates CDER, CDRH, and OCP for working together to produce this draft guidance. This is a significant step forward in providing clarity in a difficult area. In order to maximize clarity and avoid duplicate or conflicting information, PDA recommends that this new guidance be built upon the foundation of the CDRH Final Guidance: *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and/or the IEC standard: *Human Factors Engineering for Medical Devices*. This new guidance document would then only address the new issues and special considerations regarding human factors that would apply to Combination Products (CP). PDA would be happy to work with FDA to develop additional guidance which addresses usability and human factors issues for generic or interchangeable biosimilar CPs and human factors issues for connected combination products.

In addition, PDA recommends that this guidance title be changed to "Human Factors Study Considerations in Combination Product Design and Development." Given the definitions of HF and clinical studies, PDA encourages the FDA to change the references throughout the document to eliminate any confusion. HF studies and clinical studies have different purposes.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in pharmaceutical, biological and device manufacturing including members representing our Combination Products Interest Group, Regulatory Affairs and Quality Advisory Board, and Board of Directors.

If there are any questions, please do not hesitate to contact me.

Sincerely,

Richard M. Johnson

Richard Johnson, President and CEO, PDA

Food and Drug Administration Draft Guidance

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development

May 3, 2015

General Comments	Rationale	Critical?
1. PDA congratulates CDER, CDRH, and OCP for working together to produce this draft guidance. This is a significant step forward in providing clarity in a difficult area. In order to maximize clarity and avoid duplicate or conflicting information, PDA recommends that this new guidance be built upon the foundation of the CDRH Final Guidance *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and/or the IEC standard and only address the new issues and special consideration that would apply to Combination Products (CP).	This concept of this draft guidance purports to address Human Factors (HF) for CP. However, with regards to HF, it only addresses and discusses simulated use Formative HF studies and Simulated Use Validation HF Studies. Human Factors engineering starts well before these activities are implemented during the product design and development process. The entire HF process is addressed in the CDRH guidance and the IEC 62366 series of standards. By not referencing and providing that these other documents are essential to a robust HF program, this guidance could be misleading and misinterpreted that these are the only elements important to HF for CP. FDA should emphasize that the focus of this new guidance is to help provide any unique specifics on the final HF assessment requirements of the CP. In addition, this guidance only references the CDRH guidance for "related definitions". As above, the definitions in the CDRH guidance should be primary and only where there is a necessary difference for CP should a new definition be introduced with this guidance.	Y
2. PDA recommends that this guidance title be changed to "Human Factors Study Considerations in Combination Product Design and Development" and remove the word "related" which precede the multiple mentions of clinical studies throughout the guidance. Given the definitions of HF and clinical studies, PDA encourages the FDA to change the references throughout the document to eliminate any confusion. HF studies and clinical studies have different purposes.	Referring to the studies as HF and related clinical studies infers that the FDA position is that HF studies are considered clinical studies, which is not aligned with industry perspectives, or CDRH guidance on HF studies. HF studies are part of design validation, a key component of design controls which provide the framework for safe and effective use of the CP. As defined in the CDRH guidance Feb 2016, HF studies "assess user interactions with a device user interface to identify use errors that would or could result in serious harm to the patient or user…also used to assess the effectiveness of risk management measures…represents one portion of design validation." Per (ICH) E6 *Good Clinical Practice: Consolidated Guidance*, the definition of a clinical study does not include HF studies and is as follows: "Clinical trial/study: Any investigation in human subjects	Y

General Comments	Rationale	Critical?
	intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous." www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf Also see the PDA comments on FDA eCTD Technical Conformance Guide. Other organizations made similar comments to this docket. (http://www.regulations.gov/#!documentDetail;D=FDA-2015-D-3390-0011): *Human factors are design validation studies performed as part of design controls and are not clinical trials. Human factors studies do not involve active drug in an investigational manner, actual patient dosing (e.g. injection, inhalation), or the assessment of clinical effect. A human factors study evaluates the product under a simulated intended use rather than an actual intended use, and therefore is not a clinical study. It is an in-vitro assessment of usability of the of the combination product and is not a clinical assessment.*	
3. PDA recommends additional clarification and differentiation between the terms *simulated use human factors studies* and *clinical use human factors studies*. These are very different studies with significant differences in the objectives, protocols, information and execution. PDA also recommends deleting the term *Major Clinical Study* (or *Major Clinical Trial*) and	There are significant differences in the objectives, protocols, information and execution of what are three very different types of studies. ***Simulated Use Human Factors Studies*** The objective of these studies is to assess the use of the product. These are done in a simulated use fashion which means the device DOES NOT PERFORM its essential function (e.g.. in the case of a drug delivery combination product, the drug is not delivered to the patient). Only the "critical" tasks are evaluated and all of the uses are closely observed by professionals who can determine if there were use errors and can	Y

General Comments	Rationale	Critical?
instead, using terms already well-defined in agency regulation and guidance (i.e. pivotal and phase 3 clinical studies) to refer to studies for the purpose of gathering clinical safety and efficacy/effectiveness data to support marketing applications. From PDA's perspective, there is no need to introduce a new term where established terms of equivalent meaning are already known. Introduction of this term is confusing and unnecessary to understanding the intent of the guidance.	interrogate the user immediately after the study to assess the root cause of the error. ***Clinical Use Human Factors Studies*** This term is preferred over the term "Human Factors Actual Use Validation Studies" The objective of these studies is also to assess the use of the product. These are only done when a simulated use CANNOT adequately address specific use conditions or environment and would not provide representative results. In this test the device PERFORMS its essential function, but the primary objective is not to assess therapeutic success, but only use success. Only the "critical" tasks are evaluated and all of the uses are closely observed by professionals who determine if there were use errors and can interrogate the user immediately after the study to assess the root cause of the error. ***Clinical Studies Which May Provide Use Information*** These studies should be described using previously defined FDA terms such as phase 3, or pivotal, and not with the term "major clinical studies." The primary objective of these studies is to assess the therapeutic safety and efficacy/effectiveness of the product, not the use of the product. In these studies the product (device constituent part) PERFORMS its essential function, but the use of the product is not, or cannot be closely observed by a professional to determine if there were use errors and who can interrogate the user immediately after the use to assess the root cause of the error. Although information on the successful use of the product may be recorded in a log or questionnaire, it is anecdotal and is not sufficient to assess the root cause or take definitive corrective action. It is NOT a HF study. In some cases, in order to bridge from one delivery mode to another, there is a type of study where a CP will be put into an arm (some are open label) or extension of a clinical study which have been called "real use" or "actual use" studies. These may or may not collect evidence of therapeutic	

General Comments	Rationale	Critical?
	success, but are primarily to collect information on the successful operation and use of the product. Although these may provide evidence of the robustness of the CP and CP use in real clinical conditions, these are also NOT HF studies for the same reasons stated above.	
4. PDA recommends that the guidance recognize that HF studies to validate the use of clinical product in a clinical study may differ from the HF studies to validate the use of final commercial product for commercial use.	It is understood from the guidance that the FDA will require sufficient validation data or evidence to ensure that the clinical product, to be used by clinical subjects in a clinical trial environment, are safe for that use. Depending on the product, there may not need to be a validation study, per se, but may be supported by totality of evidence supporting safe use. It is also understood that the FDA will require sufficient validation data or evidence to ensure that the commercial product, to be used by patients in a commercial use environment, are safe for *that* use. However, the product, packaging, labeling, users and use conditions may necessarily vary from the clinical study to the commercial product. As such, although the structure and form of the study may be similar, a *simulated use HF validation study* of a *clinical finished combination product* will be different from the *simulated use HF validation study* of a *commercial finished combination product*. In situations where the clinical product and conditions do not change, the *simulated use HF validation study* of a *commercial finished combination product* may not be necessary or may involve a re-validation of any changed elements.	Y
5. Throughout the document there are instances where "mitigating" or "reducing" are used in reference to hazard. These terms include the element of likelihood, which is associated with "risk". It is appropriate to "eliminate a hazard", "mitigate a risk" and "reduce a risk". This use of terminology is in alignment with ISO and ICH documents that address Risk Management. PDA proposes the language be clarified throughout the draft. A few	Examples of recommended changes: • Lines 79 and 80: Incorporate and validate design features that eliminate the Hazard and/or mitigate these ~~hazards~~ **risks**. • Line 83: "For a drug product, goals for reducing use-related ~~hazards~~ **risks**. • Line 97 and 80: " … to ensure that use-related hazards associated with the product are eliminated and/or **risks** mitigated to reduce patient adverse events …" Examples of cases where it is worded correctly:	Y

General Comments	Rationale	Critical?
examples are listed here:	• Line 134 and 136: "The study should demonstrate that use-related hazards for the final finished combination product (see glossary item A.2 below) have been eliminated or that the mitigation for residual risks is acceptable" • Line 160 and 161: "…as well as to characterize high-risk hazards so they can be mitigated or eliminated through improved product interface design." (Note: this is acceptable because the text associates both hazard and risk.)	
6. PDA recommends the guidance document acknowledge that connected combination products are not specifically covered by this guidance and future guidance on this topic is still needed. In addition, PDA recommends that this guidance clearly indicate that Stand-alone software that are used with one specific drug, and are classified as CP can be fully addressed by the CDRH Guidance.	This area is growing in importance and prevalence across the healthcare stakeholder community. Many stakeholders are working to incorporate communications capabilities into combination products with the primary objective of improving outcomes. The current draft guidance does not address the HF issues specific to connected CP. Rather than recommend FDA include guidance on this topic in the final version of this document, PDA would be willing to work with the agency in drafting a new guidance for this topic as soon as possible.	Y
7. PDA agrees that this guidance can be used for Biosimilar products where the CP delivery system may differ, and therefore FDA will require sufficient HF validation data or evidence to ensure that the clinical and commercial products are safe for that use. However, this guidance does NOT address the usability of *generic* or *interchangeable biosimilar* CPs. In order to ensure the availability of generics and interchangeable biosimilar CPs, PDA recommends the guidance acknowledge that HF requirements for generic and	Human Factors for generic and biosimilar CP may be complicated, especially when considering the possibility of interchangeability where the generic/biosimilar combination product may be substituted for the originator CP by a pharmacist without the opportunity for health care provider training as indicated in the labeling of the reference product. As the current draft guidance does not address the complicated nature of HF issues specific to generic and biosimilar combination products, PDA requests the agency go through formal commenting on expanded or additional guidance for these products. PDA would be willing to work with the FDA on developing this additional guidance.	Y

General Comments	Rationale	Critical?
interchangeable biosimilar CP may extend beyond those of originator CP. PDA also recommends the Agency state the limitations of this guidance in addressing generic and interchangeable CP and develop additional guidance to detail the manner in which HF can play a role in their verification and validation.		

Specific Comments to the Text

Line No.	Current Text	Proposed Change	Rationale	Critical?
23	In addition, the guidance describes how HF studies relate to other clinical studies.	In addition, the guidance describes how HF studies relate to ~~other~~ clinical studies.	HF studies are not a type of clinical study. Please also see General Comments.	Y
65	What is the role of HF studies as compared to other types of clinical studies?	What is the role of HF studies as compared to ~~other types of~~ clinical studies?	HF studies are not a type of clinical study. Please also see General Comments.	Y
97	…should be assessed in HF studies if needed to ensure the use-related hazards associated with the product are…	…should be assessed in HF studies if needed**,** to ensure the use-related hazards associated with the product are…	PDA recommends punctuation to clarify whether the need is for the HF studies; or for the use related hazards being eliminated or mitigated.	
106 - 110	For purposes of this document, the following definitions and concepts apply to HF studies, the final finished combination product, and the major clinical study. For additional information on these terms see the sections that follow the glossary. For related definitions see Agency guidance *Applying Human Factors and Usability Engineering to Optimize Medical Device Design.*3	For purposes of this document, the following definitions and concepts apply to **Simulated Use HF Validation of Combination Products, such as *simulated use* Validation HF studies *of* the finished combination product, and any required phase 3 or pivotal clinical studies. Designers of drug delivery combination products should follow the final CDRH guidance** (*Applying Human Factors and Usability Engineering to Optimize Medical Device Design)* and the IEC 62366 series of standards to execute a complete Human Factors program as a foundation for these final verification and	This section addresses the concept of this guidance, which purports to address Human Factors for Combination products. However, with regards to Human Factors, it only addresses and discusses simulated use formative and validation HF studies. Human Factors engineering starts well before these activities are implemented during the product design and development process. The entire HF process is addressed in the CDRH guidance and the IEC 62366 series of standards. By not referencing and providing that these other documents are essential to a robust HF elements, this guidance could be misleading and misinterpreted that these are the only elements important to HF for CP. A reference to the final CDRH guidance and/or the IEC standard as the appropriate guidance to prepare and implement a robust HF program for a CP is required,	Y

Line No.	Current Text	Proposed Change	Rationale	Critical?
		validation activities.	specifying that this guidance helps provide specifics as on the final assessments of the combination.	
112	*Human Factors Study (or HF Study):* A study conducted with representative users to assess the adequacy of the combination product user interface design to eliminate or mitigate potential use-related hazards.	A study conducted ~~with representative users~~ to assess the adequacy of the combination product user interface design to eliminate ~~or mitigate~~ potential use-related hazards **or mitigate potential use related risks. This can include studies with representative users.**	Guidance should be broadened to include other types of human factors activities that may include early studies which may not involve representative users but could include input from other exercises, such as focus groups with KOLs, HF experts and studies with other user groups.	
124 (see also 306-307)	A study conducted on a combination product prototype user interface at one or more stages during the iterative product development process to assess user interaction with the product and identify potential use errors.	A study conducted on a combination product ~~prototype~~ user interface at one or more stages during the iterative product development process to assess user interaction with the product and identify potential use errors.	The study may be conducted on any type of user interface, including those from other, related products or fabricated tools not only prototypes. It is particularly important that this takes place during the development process.	
127 (also 314)	Formative studies are iterative and inform the need for user interface changes…	Formative studies ~~are iterative and~~ inform the need for user interface changes…	Formative studies themselves may or may not be iterative. They are part of an iterative design/development process (see line 124 which references an iterative product development process).	
134 - 139	The study should demonstrate that use-related hazards for the final finished combination product (see glossary item A.2 below) have been eliminated or	The study should demonstrate that use-related hazards for the ~~final~~ finished combination product (see glossary item A.2 below) have been eliminated or	See general comment on "clinical" vs. "Commercial" products and the associate use studies. Final finished product may not be needed for a clinical study.	Y

Line No.	Current Text	Proposed Change	Rationale	Critical?
	that the mitigation for residual risks is acceptable; i.e., the benefit of product use outweigh the residual risk of the product. The study participants are representative of the intended users and the study conditions are representative of expected use conditions.	that the mitigation for residual risks is acceptable; i.e., the benefit of product use outweigh the residual risk of the product **for the uses for which these products are intended. The product should be representative of the product that is intended to be used (e.g. clinical or commercial) and** the participants ~~are~~ **should be** representative of the intended users and the study conditions are representative of expected use conditions **for which these products are to be used (clinical vs. commercial). Products, participants and conditions of use in a clinical study may necessarily differ from those that will be used commercially. If there are no differences or changes after the clinical study, parts or all of the validation may be applied to the commercial products.**		
141 (see also line 583)	Final Finished Combination Product: The final finished combination product is the product intended for market and submitted in the	~~Final~~ Finished Combination Product: The ~~final~~ finished combination product is the product ~~intended for market and~~ submitted in	PDA requests more clarity around the uses and testing of "Finished Combination Products" used in clinical and development work vs. "Finished Combination Products" as intended for commercial use. Both are finished combination	Y

Line No.	Current Text	Proposed Change	Rationale	Critical?
	marketing application. 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 training programs).	**either** the marketing application **or an investigational application** . 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 training programs)**as appropriate for the phase of development where it is to be used(either clinical or commercial).**	products, but may have significant differences. See general comment on "clinical" vs. "Commercial" products.	
179-181	Critical tasks are 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.	… performed incorrectly or not performed at all, would or could cause **serious** harm to the patient or user, …	This wording is aligned with definitions and statements in FDA Guidance Applying Human Factors and Usability Engineering to Medical Devices, dated February 3, 2016, Section 2: Scope 'If the results of risk analysis indicate that use errors could cause **serious** harm to the patient or the device user, then the manufacturer should apply appropriate human factors or usability engineering processes according to this guidance document.'	
188-211	Some examples of critical tasks to illustrate this concept include: …	PDA Recommends the following additional bullets be added to this section: • **"The user being able to understand and correctly respond to visual, auditory, and/or tactile notifications.**	Device notifications, particularly alarms/alerts which are almost always mitigations to risks are not mentioned. If not understood, these notifications will lead to incorrect tasks by the user which could lead to harm.	

Line No.	Current Text	Proposed Change	Rationale	Critical?
		Failure to successfully perform this task could result in medication errors." • **The user being able to complete a series of several non-critical tasks required to prepare… Failure to successfully complete these tasks in the correct sequence could result in medication errors, and therefore the sequence becomes critical, rather than the individual task.**	It is unclear whether it is the 'sequence' of events that is making the scenario potentially critical, or the combination of multiple critical steps. We therefore propose as additional bullet.	
274	…HF study should evaluate the user interface in the absence of training.	…should evaluate **the parts of** the user interface **that pose potential for harm (critical Tasks)** in the absence of training.	The 'user interface' is defined in the FDA Guidance *Applying Human Factors and Usability Engineering to Medical Devices,* dated February 3, 2016 as ALL aspects of user interaction. It is not reasonable or required that the HF study evaluates ALL aspects of user interaction, only those that pose potential for harm.	
306-307 (see also 124)	HF Formative studies are designed to evaluate early combination product prototypes, taking into… HF Formative study results guide prototype design…	~~HF~~ Formative **Simulated Use Human Factors** studies are designed to evaluate early combination product ~~prototypes~~ **user interfaces**, taking into…. HF Formative study results guide ~~prototypes~~ **user interface** design…	The study may be conducted on any type of user interface, including those from other, related products or fabricated tools not only prototypes. It is particularly important that this takes place during the development process.	

Line No.	Current Text	Proposed Change	Rationale	Critical?
314 (see also lines 124 and 127)	Iterative HF Formative studies and related design modifications are performed until the user…	~~Iterative~~ **Formative** HF **Simulated Use** studies and design modifications are performed until the user…	Formative studies themselves may or may not be iterative. They are part of an iterative design/development process (see line 124 which references an iterative product development process).	
319	None of the individual subjects in the HF Formative Studies should participate in the HF Validation Studies	**Ideally,** none of the individual subjects in the ~~HF~~ Formative **Simulated Use HF** Studies should participate in the HF Validation Studies. **In situations where it is unavoidable, appropriate consideration should be given to avoid any bias**.	It is clear that repeat use of the same subjects should be avoided, however for certain situations (eg: orphan drugs or rare diseases where the number of patients is limited) this could occur. Additionally, this may be difficult to control whilst maintaining aspects of patient confidentiality – especially where different organizations are used to perform different studies on behalf of the Sponsor.	
337	Simulation methods for these studies vary and may include the use of a manikin, injection pads, placebo, and other elements intended to simulate the patient, the procedure, or the environment of use.	Simulation methods for these studies **are all performed in-Vitro, may** vary and may include the use of a manikin, injection pads, placebo, and other elements intended to simulate the patient, **the procedure,** or the environment of use.	Clarification that even the placebo formulation is not intended to be injected into a human participant so as to not impact the risk profile of the study.	
342-344	The conditions of the HF Simulated-Use Validation study should be sufficiently realistic so that the results HF-Simulated-Use Validation represent relevant aspects of	The conditions of the ~~HF~~ Simulated-Use **HF** Validation study should be sufficiently realistic so that the results **of a** ~~HF-~~Simulated-Use **HF** Validation represent **the intended users**	PDA recommends adding reference to "Intended User and Use Environments" should be added instead of "actual use of the product once introduced into the market". Basically the intended users and the intended use environment should be adequately represented	

Line No.	Current Text	Proposed Change	Rationale	Critical?
	actual use of the product once introduced into the market.	**and the intended use environment adequately**~~. relevant aspects of actual use of the product once introduced into the market.~~	in the study.	
361	A HF Actual Use Validation Study of the Combination Product that includes the actual drug in a simulated use setting may be necessary when the drug can affect the user's ability to perform a critical task.	A ~~HF Actual Use Validation~~ ***Clinical Use Human Factors*** Study of the Combination Product that includes delivery of the actual drug or placebo in a simulated use setting may be necessary when ~~the drug; or~~ **the presence of the drug; or the actual act of drug delivery;** can affect the user's ability to perform a critical task.	Please see additional rationale in general comments regarding study definitions.	Y
446-447	If the use-related risk analysis identifies the need for HF studies, then a HF Validation study should be conducted and the results submitted for review.	If the use-related risk analysis identifies the need for HF studies, then a HF Validation study should be conducted and the results **in support of a commercial application may be** submitted for review **prior to and/or at the time of filing the commercial application**.	Clarify that submission of data in support of a commercial application can occur prior to the filing and/or at the time of the filing. An applicant request for pre-filing review of the data is optional and at the discretion of the applicant.	
458-460; 516-517	During the investigational phase when the applicant determines that a HF Validation study may not be needed, the applicant should submit its risk	During the investigational phase when the applicant determines that a HF Validation study may not be needed, the applicant ~~should submit its risk analysis~~	Seeking Agency comment in advance of a clinical or commercial application is optional and at the discretion of the applicant. This mechanism/pathway for feedback is encouraged, however in many cases the	

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	analysis and justification to support the basis of the applicant's conclusion, and seek Agency comment on the assessment." "To facilitate discussion with FDA, the applicant should provide a proposal about what, if any, additional HF testing is needed.	~~**and justification to support the basis of the applicant's conclusion, and**~~ **can** seek Agency comment on the assessment **by submitting its risk analysis and justification to support the basis of the applicant's conclusion**. **If agency comment is solicited, the agency will target providing feedback within 60 days.**	guidance that has already been provided by the agency (as in this guidance) or the sponsor's experience is such that the company feels sufficiently confident to provide this information in the submission and not request feedback or comment before the submission. If a Pre-filling request is made FDA must have commitment to review and provide comment in a manner to promote efficient review (e.g. submission to the investigation application prior to product being used outside the health care environment or by laypersons, with a FDA target of 60 days for review and feedback). Additional details regarding submission mechanism/pathway, scenarios for pre-filing submission, and a timeframe for FDA review would improve efficiency of product development.	
461	If the syringe, needle and needle guard …	If the syringe, needle **or** needle guard…	The novelty, experience or other factors may come from <u>any</u> of the component parts of the device constituent part described here and do not need to be present in all three constituent parts.	
493 - 526	B. Considerations for Design Changes After HF Validation FDA recognizes that combination product design changes may occur premarket	B. Considerations for ~~Design~~ Changes After HF Validation FDA recognizes that changes to the combination product ~~design changes~~ may occur premarket or	PDA recommends broadening the language in this section because not all changes are design changes. Additional examples are below.	

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	or postmarket after HF Validation studies have been completed. ....Similarly, during postmarket development an applicant may plan a design change to the marketed combination product, for example, to respond to use-related safety reports, complaints/problems, to address a manufacturer-initiated postmarket corrective and preventative action plan, or to meet the needs of an expanded indication or user population.	postmarket after HF Validation studies have been completed. ...Similarly, after the product is commericalized ~~during postmarket development~~ an applicant may plan a ~~design~~ change to the marketed combination product, for example, to respond to use-related safety reports, complaints/problems, to address a manufacturer-initiated postmarket corrective and preventative action plan, or to meet the needs of an expanded indication or user population.		
503-505	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.	However, ~~design~~ changes made after HF Validation that ~~relate to identified~~ **might negatively impact the performance of 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.	There could be minor changes related to critical tasks that should not automatically trigger a revalidation study. For example, bolding a line of text in the instruction to properly dispose used product should not necessitate a new validation study.	
511	Does the design change alter the user interface in any way (e.g., audible, tactile, color recognition, user instructions, etc.)?	Does the ~~design~~ change alter the user interface in any **user perceivable** way (e.g., audible, tactile, color recognition, user instructions, etc.)?	If a change affects tactile or audible feedback but cannot be perceived by a user (normal hearing range etc.)it should not need retesting i.e. the frequency or volume of the feedback can be measured as different but not perceived by	

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			the patient.	
516 - 521	To facilitate discussion with FDA, the applicant should provide a proposal about what, if any, additional HF testing is needed. The proposal should include a detailed description of why the change is being made, a description of what specifically is changing, a use-related risk analysis of the new design, and where appropriate a proposal for evaluating potential risk mitigations of the new design and the effects of the change.	**If the change is substantive, and will require FDA approval prior to implementation,** FDA recommends the applicant provide a proposal about what, if any, additional HF testing is needed **to facilitate discussion**. The proposal should include a detailed description of why the change is being made, a description of what specifically is changing, a use-related risk analysis of the new design, and where appropriate a proposal for evaluating potential risk mitigations of the new design and the effects of the change.	There are many changes to the Combination Product before, and potentially after approval that are so minor that they would not require approval and/or submission to the FDA. This would not preclude that the company perform a risk assessment regarding this or any change, no matter how small.	
522-525	When making a change to a combination product, FDA encourages applicants to expeditiously identify the change plans and to discuss with the Agency the types of HF and other clinical or non-clinical studies that may be applicable before the applicant's approval of the design change.	When making a change to a combination product, FDA encourages applicants to expeditiously identify the change plans and **potential impact upon the Human Factors data package. Where appropriate, applicants should** discuss with the Agency the types of HF and other clinical or non-clinical studies that may be applicable before embarking upon the	Sponsors must be allowed to exercise their internal Change Control procedures uninhibited. Involvement of FDA in changes prior to internal approval is un-necessarily restrictive.	

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		activities.		
531 - 533	The combination product's specific use-related risk analysis generally informs the Agency's expectations for whether HF information on a combination product should be submitted in an investigational application. The 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 is not needed, the applicant should provide the use-related risk analysis along with the justification for this conclusion.	The combination product's specific use-related risk analysis generally informs the Agency's expectations for whether HF information on a combination product should be submitted in an investigational application. ~~The 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 is not needed, the applicant should provide the use-related risk analysis along with the justification for this conclusion.	If the company decides that a HF evaluation is required, and performs the study, the Risk assessment (RA) is not necessary to be submitted. It is only when the RA determines that no HF are required that is should be submitted to support that decision.	
536-552	If the use-related risk analysis indicates that a HF study is necessary, … When this information is submitted to the investigational application, FDA will review the information….and intends to provide comments or recommendations…	…When this information is submitted to the investigational application, FDA will review the information…….and intends to provide comments or recommendations **within approximately 60 days …**	PDA requests that FDA provide some suggested timeframe for this review to avoid delays in the product development program or clinical development program. Additional details on the regulatory submission mechanism and timing would improve efficiency of product development.	
575-578	After review of the marketing application, depending on the potential impact of resulting	After review of the marketing application, depending on the potential impact of resulting	PDA recommends clarifying the timing expectation for a revalidation study triggered by FDA labeling review comments (e.g. as post-	

Line No.	Current Text	Proposed Change	Rationale	Critical?
	labeling differences on performance of critical tasks, an additional HF Validation study may be needed to ensure that the changes minimize the use-related risks without creating additional hazards.	labeling differences on performance of critical tasks, an additional HF Validation study may be needed to ensure that the changes minimize the use-related risks without creating additional hazards. **FDA will discuss the reason/basis for the changes with the applicant and the scope and timing for any revalidation activities expected by the Agency. A risk-based justification for not performing revalidation activities prior to approval will be considered by the Agency, if appropriate.**	market commitment). If a revalidation study is required prior to Agency approval due to changes driven solely from Agency review of labeling, it could significantly delay product approval or production/launch costs. If the Agency requires modification to instructions for use validated through HF studies, discussion should occur between FDA and the applicant to ensure understanding of the reason/basis for the changes and the scope and timing of any revalidation activities expected by the Agency. The applicant should be provided opportunity to re-assess risks based on the changes and provide a justification for not completing revalidation studies, if appropriate.	