May 3, 2016

Dockets Management Branch (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 Considerations in Combination Product Design and Development

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the Draft Guidance entitled "Human Factors Studies and Related Clinical Considerations in Combination Product Design and Development" (Draft Guidance).[1]

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products.

General Comments

BIO is appreciative of FDA's efforts to provide greater clarity regarding human factors (HF) issues in the context of combination products that are comprised of a drug or biological product and a device, and "to promote the development and timely review of safe and effective combination products."[2]

Combination products are comprised of any combination of a drug, device or biologic product (e.g., drug-device, biologic-device, drug-biologic, or drug-device-biologic). Each constituent part of a combination product retains its original regulatory status and, therefore, the combination product is subject to the unique regulatory requirements applicable to each of its constituent parts.

Advances in personalized medicine and new drug delivery technologies have led to an ever-increasing number of combination products being co-developed to meet unmet needs. However, the FDA review structure on which Sponsors rely is one that was established at a time when products were being developed individually, which had led to redundancies and inconsistencies in the review of combination products.

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[1] FDA Draft Guidance For Industry, *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development* (February 3, 2016), FDA Docket No. FDA-2015-D-4848.
[2] Draft Guidance, p2.

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Greater clarity and alignment of the regulatory requirements applicable to the constituent parts, and coordination between centers during the review of a combination product is absolutely essential to timely and efficient review of these products.

We greatly appreciate recent steps taken by the Agency to provide greater efficiency, consistency and predictability in the review of combination products.[3] BIO believes that this Draft Guidance will provide additional clarity to sponsors related to HF studies in the development of combination products.

We offer specific comments on the Draft Guidance below, and in the accompanying chart, around several main themes: the need to ensure consistency with existing guidance and regulations regarding medical devices; clarification that HF studies are not clinical studies; and concerns with potentially shifting accountability for design control, risk assessment and change control from the applicant to the FDA.

Specific Comments

1. Consistency with Existing Guidance and Regulation Governing Medical Devices

BIO understands that the Draft Guidance is meant to complement the recently issued FDA Final Guidance entitled "Applying Human Factors and Usability Engineering to Medical Devices: Guidance for Industry and FDA Staff" (Device HF Final Guidance), issued February 3, 2016.[4] While we are pleased to see the collaboration between the Office of Combination Products and the Centers in preparing this guidance to industry on the special considerations for human factors information submitted in investigation and marketing applications, we would like to better understand what unique information this new guidance provides, and how it aligns with the Device HF Final Guidance as well as other existing guidance documents and standards related to human factors.

For combination products, many of the same principles for HF studies apply as for devices, such as the planning process (identifying intended users and use environments before critical task identification), the use of commercially-equivalent product in the HF Validation study, and the simulation of an actual use environment including training if applicable. It is unclear why a combination product should be managed differently or why the review process for these studies should be any different than for a device. Many of our comments address instances where terminology in this guidance is defined differently than in other documents (e.g., "critical task"), or where information found elsewhere could not be found in this draft guidance. Closer alignment between this guidance and existing documents may help prevent increase in time or duplication of efforts by both applicants and FDA, for example, by increasing the scope, formality, and time for investigational and marketing application reviews.

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[3] http://blogs.fda.gov/fdavoice/index.php/2016/03/leaning-in-on-combination-products/ (March 7, 2016) http://blogs.fda.gov/fdavoice/index.php/2015/10/the-merging-of-medical-products-enhancing-review-of-therapeutic-and-diagnostic-combination-products/ (October 25, 2015)

[4] FDA Draft Guidance For Industry and Food and Drug Administration Staff, *Applying Human Factors and Usability Engineering to Medical Devices* (February 3, 2016).

2. Human Factors Studies Are Not Clinical Studies

The Draft Guidance should clarify that an HF study should not generally be considered a clinical study unless it meets the specific definition of a clinical study. The repeated references to HF studies "and other clinical studies," as well as other similar statements, raise concerns that the Draft Guidance is implying that an HF study is a type of, or minor, clinical study.[5] As the Device HF Final Guidance notes, HF data can be collected as part of a clinical study, but an HF study is not the same as, nor a type of clinical study[6].

Under the *International Conference on Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) E6 Good Clinical Practice* Consolidated Guidance, which is recognized by the FDA, the definition of a clinical study is:

> "Clinical trial/study: Any investigation in human subjects 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."[7]

There are distinct differences between the objectives and endpoints of human factors studies versus clinical studies. Whereas a clinical study assesses the safety and efficacy of a drug product for a proposed indication, an HF study of a drug-device combination product assesses the safety and efficacy of the user interface of a combination product regardless of the safety or efficacy of the drug product.

Unless HF data is collected as part of a clinical study, an HF study does not use the same type of study materials as does a clinical study: a clinical study involves the clinical use of actual active drug products, whereas an HF study uses samples without active drug product or active drug product use assessed without delivery to a human (*e.g.*, use of an injection training pad, an aerosol/spray delivery to a controlled space or a device without its drug constituent part).

Most importantly, an HF study has predetermined participant demographics, may involve a range of user training conditions, and relies on HF behavioral experts to observe task deviations, user errors, near misses/close calls, and operational difficulties, and to conduct knowledge probes about them. These study elements are typically not possible in clinical studies or home use studies.

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[5] For example, "...[T]he guidance describes how HF studies related to **other** clinical studies." [Emphasis added]. Draft Guidance, lines 22-23. This use of the word "other" would suggest that an HF study is a type of clinical study.
[6] See: Final Device HF Guidance, Section 8.3.
[7] ICH E6 Good Clinical Practice Consolidated Guidance, at 3 (Definition 1.12). Available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf

To ensure clarity and consistency in the use of terminology, the term "clinical study" should not be used to describe an HF study, and the Agency should make clear that an HF study is not a clinical study.

The regulatory implication of considering an HF Study to be a clinical study is that, for any device modifications validated with an HF study, filing supplements may be considered to be efficacy Prior Approval Supplements, with longer review times and submission costs. Additionally, as implied in footnote 7 in the draft guidance, to consider an HF study to be a type of clinical study would require a case-by-case decision about whether PDUFA User Fees apply. We recommend that the final guidance address the type of drug supplement appropriate for a device change that is supported with HF study data.

3. Accountability for Reviewing Design Changes, Determining Necessity of HF Studies, and Appropriate Tasks and Study Users

We appreciate the intent of the Draft Guidance to answer questions specific to combination products, and, as described in the Introduction and Scope, the intention to promote timely review of combination products. However, we are concerned with language that implies that the FDA should assume responsibility for reviewing design changes, determining whether HF studies are necessary, and determining appropriate tasks and study users.[8] Such a transfer of accountability from applicants to the FDA would place an increased burden on the Agency, which may translate to a longer application review than necessary or what is currently expected for devices.

BIO urges the Agency to clarify in the Draft Guidance that, while Sponsors have the option to consult the Agency regarding the types of HF studies and clinical and non-clinical studies that may be applicable prior to approving potential design changes, such consultation is not required. The ultimate accountability for reviewing design changes, determining necessity of HF studies, and determining appropriate tasks and user studies rests solely with the Sponsor.

BIO also recommends that the Draft Guidance place more emphasis on the use of formative study results to inform decisions related to design change review and the applicability of HF studies. Per existing CGMP requirements for combination products[9] and design control requirements for medical devices[10], applicants are already expected to make risk-based decisions that are most appropriate for their products and target users and validating that the user interface of a combination product is effective via testing under actual or simulated use conditions.

BIO appreciates the opportunity to provide comments to the Draft Guidance entitled "Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and

[8] See Draft Guidance at lines 522-525.
[9] 21 C.F.R. Part 4.
[10] 21 C.F.R. 820.30(g).

Development." We provide additional specific, detailed comments to improve the clarity of the Draft Guidance in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely

/S/

Cartier Esham, Ph.D.
Executive Vice President, Emerging Companies Section &
Vice President, Science & Regulatory Affairs
Biotechnology Innovation Organization

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION AND SCOPE		
Lines: 1-2	As stated in the Specific Comments section above, HF studies are not the same as, nor a type of clinical study.	"Human Factors ~~Studies and Related Clinical~~ Study Considerations in Combination Product Design and Development."
Lines: 22-23	As stated in the Specific Comments section above, HF studies are not the same as, nor a type of clinical studies.	"In addition, the guidance describes how HF studies related to ~~other~~ clinical studies."
II. BACKGROUND		
Lines: 65	As stated in the Specific Comments section above, HF studies are not the same as, nor a type of clinical studies.	"What is the role of HF studies as compared to ~~other types of~~ clinical studies?"
Lines: 71, Footnote 7, last line	As stated in the Specific Comments section above, HF studies are not the same as, nor a type of clinical studies. Therefore, in considering HF studies in User Fee determination, an HF study should only be considered a "clinical study" to the extent that the objectives, interventions or study materials are the same as those of a clinical trial of a drug product or placebo to human subjects.	"~~As applicable, FDA will determine whether a HF study would meet these criteria.~~ Whether a HF study would meet these criteria depends on whether the objectives, interventions, or study materials are the same as those of a clinical trial, for instance, if the study protocol involves actual delivery (e.g., injection) of drug product or placebo to humans."
Lines: 74-75	Edited to provide greater clarity.	"[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."

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III. HUMAN FACTORS		
A. Glossary and Concepts		
Lines: 112, 116	The current definition of Human Factors Study (or HF study) is narrower than defined in the ISO 62366 standard, which is inclusive of more than just usability. BIO recommends clarifying that, for the purposes of the Draft Guidance, "HF Study" refers to "usability studies."	Line 112: "1. *Human Factors Study (or HF Study):* A study of human capabilities (physical, sensory, emotional, and intellectual) and limitations to the design and development of devices, systems, and environments.[A] An HF study that assesses usability studies the characteristics of the user interface that establish effectiveness, efficiency, ease of user learning and user satisfaction.[B] Other HF studies include heuristic reviews, user inquiries, diary studies, and ethnographic research. HF studies are conducted with representative users..." Line 116: "A usability study~~HF study~~ evaluates (i) the ability..." [A] ANSI/AAMI HE75:2009 [B] ISO/IEC 62366-1:2015
Lines: 131-139	The definition of HF Validation Study should be aligned with the definition of the same term in the Device HF Final Guidance (section 8, page 20-21), which distinguished an HF study from a clinical study. Additionally, the definition of HF Validation Study in the Draft Guidance should include the same footnote related to "HF Summative Study" that was included in the Device HF Final Guidance. The Glossary should include HF Actual-Use	"*HF Validation Study*: A study conducted to demonstrate that the final finished combination product user interface can be used by intended users without pattern of serious use errors or problems, for the product's intended uses and under the expected use conditions.[A] 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 as low as reasonably practicable and acceptable as determined by the risk assessment process; i.e., the benefit of product use outweighs the residual risk of the product. The study

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	Validations Studies and HF Simulated-Use Validation Studies, which were defined later in the document, but were not captured in the Glossary. These definitions should clarify that a HF Simulated-Use Validation study is not considered a clinical study, and that HF Actual-Use Validation studies are not considered to be clinical studies unless they meet the definition of a clinical trial. Lastly, the draft guidance could be read that a failure for a user to perform a critical task would constitute a failed HF validation study, which is misleading. The risk management process informs the acceptance of the residual risk. In a HF validation study, it is reasonable for a sponsor to demonstrate that (a) further reduction of the use-related risks are not practical or possible, (b) the benefit outweighs the residual risk, and (c) there is no pattern of serious use errors. This approach aligns with the Device HF Final Guidance document, which states: "This section should discuss any residual use-related risk that remained after the human factors validation testing. If applicable, this section should provide a sound rationale that modifications to the user interface (including the device and the labeling) would not further reduce risk, are not possible or not practicable, and the remaining residual use-related risks are outweighed by the benefits derived from use of the device".	participants are representative of the intended users and the study conditions are representative of expected use conditions. HF validation testing is generally conducted under conditions of simulated use, but when necessary, HF data can also be collected under conditions of actual use or as part of a clinical study. [A]Human factors validation testing is sometimes referred to as "summative usability testing." However, summative usability testing can be defined differently and some definitions omit essential components of human factors validation testing as described in this guidance document."

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	BIO recommends that FDA to clarify the description of the HF validation studies in the Draft Guidance so that it aligns with the Device HF Final Guidance.	
Lines: 141	BIO recommends providing greater clarity regarding the term "final finished." The guidance should align the definition of those terms with those defined in 21 CFR Part 4 and Part 820.30(g). "Final" might be interpreted to mean the final design tested in Design Validation or the final finished product that is produced from a validated production line. "Final" might also be confused with similar terms, such as "finished" device, considered per 21CFR Part 4 as a device that is a constituent part of a combination product. For the purposes of the phrase "or their equivalents", samples used in a HF Study can be representative of a final finished device and still undergo manufacturability changes that have no impact on function as assessed in bench testing.	"*Final Finished Combination Product:* The final finished combination product is the product intended for market and submitted in the marketing application. The final finished combination product may include 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 must be representative in use and risk to those of the expected commercial product. 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)."
Lines: 147-153	As stated in the Specific Comments section above, HF studies are not the same as, nor a type of clinical studies. The definition of "Major Clinical Study" should be revised to clarify that HF studies and clinical studies have different objectives, though that, under certain circumstances (e.g., actual use HF validation studies), HF data may be collected in the context of a clinical study.	"3. ~~Major~~ Clinical Study (or ~~Major~~ Clinical Trial): ~~As opposed to a HF study, a major clinical study is a larger scale clinical study that occurs during a later phase of combination product development. Major clinical studies provide the primary support for the safety and effectiveness of a product for a proposed indication (e.g., adequate and well-controlled studies). In addition to adequate and well-controlled studies, other types of later phase larger scale clinical studies may also be considered major clinical studies; e.g., a long-term extension study. .~~" While HF validation testing is generally conducted under conditions of simulated use, when necessary, HF data can also be collected under conditions of

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		actual use, or as part of a clinical study.[A] HF studies are not, however, a type of clinical study. A clinical study (or clinical trial) assesses the safety and efficacy of a drug product for a proposed indication, whereas a HF study assesses the safety and efficacy of the user interface of a device or combination product. [A] Device HF Final Guidance."
B. Evaluation of Use-Related Risk		
Lines: 177-218	Identification and categorization of tasks as "critical tasks" should occur, as noted in line 221, after identifying users and use environment for the combination product. BIO recommends that the Draft Guidance describe the HF study planning process in the same order as it is conducted in typical development practice, and as described in the Device HF Final Guidance.	BIO suggests reordering the section, such that current subsection B.2 (Intended Users and Use Environments) precedes current subsection B.1 (Intended Users and Use Environments).
Lines: 179-181	The definition of "critical tasks" should be aligned with that of the Device HF Final Guidance, which defines a critical task as a user task "that, 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." Additionally, Sponsors should be encouraged to conduct iterative formative studies to inform the design, risk analysis, and identification of hazards and potentially critical tasks, and to revisit risk	"The use-related risk analysis should identify critical tasks. Previously unidentified risks observed during Human Factors formative studies should be included in the risk analysis and may serve to identify additional critical tasks. Critical tasks are user tasks that, 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."

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	analysis results after a formative study to help determine the need for and scope of a HF Validation study.	
Lines: 191-211	Device notifications, particularly alarms and alerts which are usually mitigations to risks, are not mentioned. These notifications, if not understood, will lead to incorrect tasks by the user which would lead to harm. Additionally, some combination products may include software components which are critical to the safe use of the product. BIO recommends adding an additional bullet in the list of examples of critical tasks to illustrate these types of critical task.	In the list of examples of critical tasks, BIO recommends adding two additional bullets stating: "• The user being able to understand and correctly respond to visual, auditory, and/or tactile notifications. Failure to successfully perform this task could result in medication errors. • The user being able to appropriate work with a software application that can affect the product."
Lines: 222-224	Similar to how the Device HF Final Guidance identifies the dependence of usability on "comorbidities (i.e. multiple conditions or diseases)," BIO recommends that the Draft Guidance point out that an important characteristic of a user group, particularly for a drug-delivery combination product, 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.	"Intended users may be categorized into distinct user groups by their difference 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."

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Lines: 269-274	The Draft Guidance states: "On the other hand, if 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, before the first use of the combination product. 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." There may be circumstances under which Sponsors anticipate that users will routinely receive training, but the Sponsors cannot guarantee it. The Draft Guidance should provide additional clarity in such circumstances. Additionally, to more closely follow the Device HF Final Guidance, "training provided to the human factors validation test participants should approximate the training that actual users would receive" (Sec. 8.1.4); trainers or additional materials accompanying an IFU that would not be required to be used prior to using the product, should not be required in a HF study. Conversely, even if the proposed labeling indicates training is required, applicants who make a risk-based decision not to include an untrained study group should not then be mandated to include untrained subjects, as has been our experience with combination product HF studies.	We recommend that the Draft Guidance provide additional clarity related to situations in which a Sponsor expects that users will routinely receive training, but cannot guarantee it. Additionally, we recommend the following addition to the text: "On the other hand, if 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, before the first use of the combination product. 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. If it is anticipated that most or all users would receive minimal or no training, then the test participants in the human factors validation test should not be trained. Untrained subjects are not required if it has previously been determined that untrained users will have increased difficulty using the product; therefore, the need for training will be specified in the product labeling."

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Lines: 298-299	The Draft Guidance states: "If the risk analysis shows that training decay is a source of use-related error, then the HF study design should evaluate the effect of training decay." Sponsors would benefit from addition clarity, provided by examples of a situation in which an HF study should simulate training decay, and a situation in which a HF study need not simulate training decay.	BIO recommends that the Draft Guidance provide examples to illustrate circumstances under which HF studies would be expected to simulate training decay and evaluate the effect of this decay, and circumstances where a HF study need not simulate training decay.
C. Human Factors Formative Studies		
Lines: 306-307; 346-348	Information on risk consideration and hazard identification provided for HF Simulated-Use Validation studies applies to HF Formative studies as well.	"HF Formative studies are designed to evaluate early combination product prototypes, taking into consideration the identified use-related ~~hazards,~~ risks, and to provide for the identification of any unanticipated hazards or unexpected use behaviors.
Lines: 312, 318	Applicants should be encouraged to conduct formative studies to shape the design, risk analysis, and identification of hazards and potentially critical tasks and to revisit risk analysis results after a formative study to help determine the need for and scope of a HF Validation Study.	Line 312: "…clinical study, or after finalizing commercial plans.). The study design should provide for the identification of any unanticipated hazards or unexpected use behaviors that were not previously identified." Line 318: "The results of HF Formative studies should inform the design of the final finished combination product and are inputs to the initial risk analysis and identification of critical tasks."
D. Human Factors Validation Studies		
Lines: 357-359	The Draft Guidance states: "HF Actual-Use Validation studies either (1) use the final finished combination product (including the drug, not a placebo) in a simulated use setting or…"	BIO recommends that the Draft Guidance clarify the definition of HF Actual-Use Validation study. Such definitions should be added to Section III.A Glossary and Concepts.

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	The distinction between a HF Simulated-Use Validation study and definition (1) of HF Actual-Use Validation study is not clear. For example, if drug is used instead of placebo but the injection is into an injection pad, would that be an HF Simulated-Use or an Actual-Use study?	
Lines: 369-380	In order to provide greater clarity to Sponsors, BIO recommends that the Draft Guidance provide an example of HF Actual-Use Validation Study in a real environment of use. Additionally, FDA should specify whether an actual drug would be used, and whether it would be administered to a human.	
Line: 380, Footnote 11	Footnote 11 states: "The term "HF Actual-Use Validation study" has a different meaning than similar terms such as "user study" or "actual use study". The term "HF Actual-Use Validation study" applies to only the evaluation of the user interface and associated critical tasks. In contrast, the terms "actual use" or "user study" (without the "HF" qualifier) often refer to clinical studies such as a major clinical study to evaluate safety and effectiveness of prolonged home use or to an open label safety study. Those studies have different purposes or mixed purposes and are outside the scope of this document. FDA recommends against referring to these different or mixed purpose studies as HF studies."	BIO recommends the Draft Guidance provide definitions for "actual use study" and "user study." Such definitions should be added to Section III.A Glossary and Concepts.

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	This footnote provides a general description for "actual use study" and "user study", but it would be helpful to include specific definitions to facilitate understanding of the distinction.	
E. Human Factors Knowledge Task Studies		
IV. PROCESS CONSIDERATIONS		
A. Considerations for Submission of Combination Product Human Factors Study Data		
Lines 440-444	The Draft Guidance states: "For the following two groups of combination products, generally human factors data should be submitted: (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 products having a device constituent part for which human factors data should be submitted. For combination products that do not fall within these two categories, a risk analysis for the combination product should be completed and the use-related risks reviewed to assess the need for HF studies (see section III.B). 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." The first group is combination products for use outside the healthcare environment, such as at home. Many types of OTC combination products which are not reviewed in applications are used outside the healthcare environment. Therefore, while the Scope of this draft guidance does state that the	The Draft Guidance should provide additional clarity related to the second category of combination products for which HF data should generally be submitted. Additionally, the Draft Guidance should clarify that the need for HF studies should be based on the use-related risk assessment for the combination product, and if the use-related risk analysis indicates that HF studies are not needed, Sponsors need not undertake such studies. Lastly, the Draft Guidance should clarify the exclusion of OTC combination products by adding a statement to the Introduction and Scope: "This guidance does not apply to combination products containing nonprescription drugs marketed without an approved application (e.g. under a monograph)."

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	focus is combination products reviewed in an investigational or marketing application, we recommend adding an explicit exclusion. The second category referenced in the above passage is unclear. Additionally, the statement that a risk analysis should be performed is applicable to all manner of products, and as stated later in the guidance, the risk assessment should determine whether HF studies are needed.	
Line: 458-460	The Draft Guidance States: "During the investigational phase when the applicant determines that a HF Validation study may not be needed, the applicant should submit its risk analysis and justification to support the basis of the applicant's conclusion, and seek Agency comment on the assessment." Additional details on the regulatory submission mechanism and timing would improve efficiency of product development.	BIO recommends providing the appropriate timing and mechanism to submit the risk analysis to promote efficient review (e.g., submission to the investigation application prior to product being used outside the health care environment or by laypersons).
B. Considerations for Design Changes After HF Validation		
Lines: 503-505	The Draft Guidance states: "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." There could be minor changes related to critical tasks	"~~However,~~ Applicants should determine, via their risk analysis procedures, whether 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."

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	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.	
Lines: 516-517	The Draft Guidance States: "To facilitate discussion with FDA, the applicant should provide a proposal about what, if any, additional HF testing is needed." As stated above, additional details on the regulatory submission mechanism and timing would improve efficiency of product development.	BIO recommends providing the appropriate timing and mechanism to submit the risk analysis to promote efficient review. Furthermore, BIO recommends clarifying that Sponsors are not required to seek advice from the FDA regarding whether additional HF testing is needed, by adding the following line before line 516: "If applicants determine there is ambiguity about whether additional HF testing is needed, they can (but are not required) to seek advice from FDA. "
Lines: 522-525	The Draft Guidance States: "When making a design 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 changes." Adding a time-consuming step of preparing briefing documents and scheduling/conducting formal meetings is not feasible when design changes are typical and frequent in the development process and when there is already a process in place to manage these changes. The request for a summary of changes made to the device during the formative studies (i.e. during device development) goes beyond	"~~When~~ If after making a design change to a combination product, applicants are unclear about what ~~FDA encourages applicants to expeditiously identify the change plans and to discuss with the Agency~~ the types of HF, ~~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 the~~ design changes are validated."

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	the information typically 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 a HF study. A comprehensive list and discussion of design changes made in response to these historical studies and design changes made for other reasons (such as material or manufacturing changes), may be burdensome and may not effectively explain why the final design was chosen and studied in the HF Validation Study. Additionally, as stated in the Specific Comments section above, HF studies are not the same as, nor a type of clinical studies.	
C. Review of Human Factors Information in Combination Product Investigational Applications		
Line: 546	Per the Device HF Final Guidance, BIO agrees the user interface of the products tested in the HF Validation study should represent the final design. However, the requirement to include "intend to market" labeling may not be feasible. Regulatory submissions for combination products regulated as drugs are often prepared months or years before a product is launched and changes may be made in labeling between the investigational stage and commercial launch. Applicants should then be able to make the determination whether the label change warrants any additional usability testing. Final labeling may not be in place at such an early	BIO recommends the removal of the requirement to include "intend to market" labeling. "~~• Intend-to-market labels and labeling (including instructions for use if any are proposed that will be tested in the HF Validation study).~~"

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	investigational application stage since studies may not have been conducted to develop them; if labeling is to be included in a HF study it may likely be draft labeling. Carton labeling is not finalized until a product is submitted for approval and text font and placement is often revised by FDA in its final review.	
D. Review of HF Studies and Certain Labeling in Marketing Applications		
Line: 576-578	The Draft Guidance states: "… An additional HF Validation study may be needed to ensure that the changes minimize the use-related risks without creating additional hazards." 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.	BIO Recommends that the Draft Guidance clarify the timing expectation for a revalidation study triggered by FDA labeling review comments (e.g., as post-market commitment).
V. RELATIONSHIP OF HUMAN FACTORS AND MAJOR CLINICAL STUDIES OF THE COMBIATION PRODUCT		
Lines: 583-584	21 CFR Part 820.30, related to design controls, does not specifically require an HF study; therefore, BIO recommends replacing the term "design controls" with "development" to provide clarity.	"…HF studies of a combination product are conducted as part of the product ~~design controls~~ development process."
Line: 586-591	As stated in the Specific Comments section above, HF studies are not the same as, nor a type of clinical studies.	"However, the HF Validation study is not sufficient to establish the safe~~ty~~ and effective~~ness~~ use of the combination product for the proposed indication. Specifically, data from the ~~major~~ clinical study(ies) establish the combination product's safety and effectiveness for the proposed indication and the complete labeling summarizes the essential scientific information needed for the safe and

SECTION	ISSUE	PROPOSED CHANGE
		effective use of the product."
Lines: 593-599	The Draft Guidance states: "Therefore, ideally, before conducting the major clinical study(ies), the HF Validation study should be conducted on the final finished combination product, including the user interface (e.g., instructions for use, training materials, and any other user labeling, if applicable). The HF Validated product would then be ready for further evaluation in the major clinical study(ies) that will be submitted in the marketing application. Noting that in some cases it may be appropriate to conduct your human factors studies in parallel to your major clinical studies or after your clinical studies to address modifications to your product." BIO notes that it is often not necessary to perform HF validation prior to inclusion of the product in a pivotal clinical study when the benefit-risk profile of the product is sufficient to support safe use of the product in a clinical study. HF Validation is not necessary prior to clinical use when HF evaluation and use-related risk analysis concludes that a combination product is suitable for clinical use. Knowledge gained from the clinical study may inform refinement to the user interface of the combination products, which may necessitate further use risk analysis and/or additional HF study. Additionally, combination products being studied in a pivotal clinical study are still under development and	"~~Therefore, ideally, before conducting the major clinical study(ies),~~ Applicants should complete risk analyses and determine that a combination product is safe for the intended clinical use prior to the clinical study. Provided sufficient evidence is available to support the proposed clinical use, it is generally appropriate to conduct the HF Validation study ~~should be conducted~~ on the final finished combination product, including the user interface (e.g., instructions for use, training materials, and any other user labeling, if applicable), after or in parallel to the clinical study(ies), prior to the regulatory filing. ~~The HF Validated product would then be ready for further evaluation in the major clinical study(ies) that will be submitted in the marketing application. Noting that in some cases it may be appropriate to conduct your human factors studies in parallel to your major clinical studies or after your clinical studies to address modifications to your product."~~

SECTION	ISSUE	PROPOSED CHANGE
	may not yet have final production units, labeling and packaging available to meet HF Validation requirements. BIO believes that it is more appropriate to conduct the HF validation study using the product and labeling representative of the final combination product configuration prior to regulatory filing (i.e., BLA/NDA/PMA, etc.) to ensure that use-related risks have been eliminated or mitigated adequately and the product conforms to the commercial intended use.	
VI. HOW TO OBTAIN ADDITIONAL INFORMATION		
APPENDIX A		
Table 1		
Lines: Title, General Comment	The title of the Table refers to "critical tasks," however, the "criticality" of the task will be dependent on the use-related risk assessment. Additionally, all of the examples provided relate to sub-cutaneous administration. Sponsors would benefit from additional examples beyond subcutaneous injection scenarios.	"Table 1: Examples of ~~Critical~~ Tasks for Combination Products that Deliver Dose by Injection"
Table 2		
Lines: Title	The title of the Table refers to "critical tasks," however the "criticality" of the task will be dependent on the use-related risk assessment.	"Table 2: Examples of ~~Critical~~ Tasks for Combination Products that Deliver Dose by Inhalation"