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

---

Draft Guidance for Industry and FDA Staff

This guidance document is for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this guidance are available from the Office of Combination Products website at http://www.fda.gov/CombinationProducts/default.htm.

For questions on the content of this guidance, contact the Office of Combination Products at combination@fda.gov or patricia.love@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health,
Center for Drug Evaluation Research,
Center for Biologics Evaluation and Research, and
Office of Combination Products in the Office of the Commissioner

February 2016

Table of Contents

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development[1]

Draft Guidance for Industry and FDA Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION AND SCOPE

This document provides guidance to industry and FDA Staff on the underlying principles of human factors (HF) studies during the development of combination products as defined under 21 CFR Part 3. This guidance describes Agency recommendations regarding HF information in a combination product investigational or marketing application and clarifies the different types of HF studies; the recommended timing and sequencing of HF studies; and how HF studies are part of the process to maximize the likelihood that the combination product user interface is safe and effective for use by the intended users, uses, and environments. In addition, the guidance describes how HF studies relate to other clinical studies. The guidance also provides process considerations for HF information in investigational or marketing applications to promote development and timely review of safe and effective combination products.

This guidance focuses on HF issues related to combination products that are comprised of a drug or biological product and a device (also referred to in this guidance as medical device) for review in an investigational or marketing application submitted to the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), or the Center for Drug Evaluation and Research (CDER). The application types include an investigational device exemption application (IDE), an investigational new drug application (IND), biologics license application (BLA), new drug application (NDA), or premarket approval application (PMA). However, the principles and recommendations may be applicable to combination products reviewed under other types of applications (e.g., premarket notification (510(k)) or abbreviated new drug application (ANDA)) as appropriate.[2]

[1] This guidance has been prepared by the Office of Combination Products in the Office of Special Medical Programs in the Office of the Commissioner in association with the Center for Biologics Evaluation and Research, the Center for Drug Evaluation and Research, and the Center for Devices and Radiologic Health.

[2] The applicability of HF studies for certain combination product design changes under the 510(k) or ANDA program are beyond the scope of this document. Applicants who are considering whether the combination product design change would change the center assignment should contact the Office of Combination Products (combination@fda.gov) for questions on the center assignment. For information on the application types within a center, contact the respective center jurisdiction officers at CDERproductjurisdiction@fda.hhs.gov , CDRHproductjurisction@fda.hhs.gov, or cberombusmana@fda.hhs.gov. Applicants preparing to submit a combination product for review under an ANDA that may include HF studies should contact the CDER Office of

Related information is available in the Agency Guidance *Applying Human Factors and Usability Engineering to Optimize Medical Device Design*[3] and the Agency Draft Guidance *Safety Considerations for Product Design to Minimize Medication Errors.*[4] Additionally, this guidance supplements other existing guidance documents developed by CBER, CDRH, CDER, and the Office of Combination Products (OCP) that describe other aspects of product development. (See Section VI for a list of some additional guidance documents.)

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Combination products, as described in 21 CFR Part 3, are comprised of any combination of a drug and a device; a device and a biological product; a biological product and a drug; or a drug, a device, and a biological product.[5] The constituent parts of a combination product retain their regulatory status (as a drug, device, or biological product) after they are combined. Accordingly, a combination product remains subject to the regulatory requirements associated with its constituent parts.

Generally, HF studies are conducted to evaluate the user interface of a product. FDA often receives requests to clarify how HF concepts apply to the development of a combination product when one of the constituent parts is a device. Inquiries include:

- What types of HF studies might need to be conducted for the combination product?
- When is the appropriate time to perform HF Validation studies?
- What is the role of HF studies as compared to other types of clinical studies?
- Are additional HF studies necessary when the design of the combination product changes?

Other general inquiries relate to regulatory considerations for combination products such as when a HF study is subject to review and approval by an institutional review board (IRB),[6] and how HF studies are considered in User Fee determinations.[7]

Generic Drugs at GenericDrugs@fda.hhs.gov regarding controlled correspondence subject to the Generic Drug User Fee Act (GDUFA) performance goals to discuss considerations related to HF studies.

[3] Guidance for Industry and FDA Staff, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design*, accessible at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM259760.pdf.

[4] Draft Guidance *Safety Considerations for Product Design to Minimize Medication Errors, accessible at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf. FDA's draft guidance documents represent FDA's proposed approach on the topics.

[5] For purposes of this document the term "drug" also refers to biological products unless otherwise indicated.

[6] Clinical studies regulated under 21 CFR Part 312 (IND requirements) or Part 812 (IDE requirements) and clinical studies intended to support an investigational or marketing application are subject to applicable requirements under 21 CFR Parts 50 and 56. *See* 21 CFR 50.1(a), 50.20, 56.101(a), and 56.103. As used in this document, clinical

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 the device will be safe and effective for use by the intended users, for the intended uses, and for the intended use environments. Under the medical device design control requirements described in 21 CFR 820.30, design validation must include a risk analysis where appropriate. As part of the risk analysis, device manufacturers should identify and analyze potential use-related hazards, including lessons learned from reported errors with similar products, and as appropriate, incorporate and validate design features that mitigate or eliminate these hazards. This assessment informs the device design development to eliminate or minimize use errors that could cause harm or compromise medical treatment.

For a drug product, goals for reducing use-related hazards are reflected in the process and data that support selection of the drug formulation, assurance of product quality,[8] drug risk management activities,[9] and in pharmaceutical quality system principles.[10] Drug development should take into account the user interface and factors that can reduce the risk for medication errors; i.e., features to enhance patient safety. Such features include product appearance, identification markings (such as imprint codes on solid oral dosage forms), container closure, packaging configurations, labeling (including labels on containers and cartons), and nomenclature.[11] The Prescription Drug User Fee Act IV (PDUFA IV)[12] provides that one of the development goals is to ensure drug safety by prospectively designing a drug that minimizes the risk for errors made by intended end users.[13]

---

study has the same meaning as investigation or clinical investigation as defined in Parts 50, 56, 312, and 812, as applicable.

[7] For information on user fee assessment under the Prescription Drug User Fee Act (PDUFA) for applications containing clinical studies, see FDA Guidance *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees* accessible at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf. As described in that document the term "*clinical data*, for purposes of assessing user fees, encompasses a broad range of studies that are purported to be adequate and well-controlled investigations submitted in support of approval. This includes [1] study reports or literature of what are explicitly or implicitly represented by the applicant to be adequate and well-controlled trials for safety or effectiveness; or [2] reports of comparative activity (other than bioequivalence and bioavailability studies), immunogenicity, or efficacy, where those reports are necessary to support a claim of comparable clinical effect. As applicable, FDA will determine whether a HF study would meet these criteria.

[8] See *Guidance for Industry Q8(R2) Pharmaceutical Development* accessible at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073507.pdf

[9] See *Guidance for Industry Q9 Quality Risk Management* accessible at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073511.pdf .

[10] See *Guidance for industry Q10 Pharmaceutical Quality System* accessible at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073517.pdf.

[11] As defined in FD&C Act section 201(m), "labeling" means "all labels and other written, printed, or graphic matters (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." As defined in FD&C Act section 201(k), "label" means "a display of written, printed, or graphic matter upon the immediate container of any article."

[12] See information under Item-IX accessible at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119243.htm.

[13] Measures for designing such a drug could address, among other things, concerns regarding: look-alike and sound-alike proprietary names; unclear label abbreviations, acronyms, and dose designations; and other label and packaging design that may lead to user error.

For a combination product that includes drug and device constituent parts, both the device design control requirements and drug development expectations apply to the entire combination product.[14] Therefore, when evaluating a combination product, the design of the product user interface should be assessed in HF studies if needed to ensure that use-related hazards associated with the product are eliminated or mitigated to reduce patient adverse events and medication errors attributable to use-related errors. This document focuses on human factors considerations for combination products to promote consistency in their design, development and review.

III. HUMAN FACTORS

A. Glossary and Concepts

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]

1. *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. Typically, HF studies are part of an iterative design process that is driven by the complexity of the combination product and the nature of the safety considerations. The HF study evaluates: (i) the ability of the user to perform critical tasks, and (ii) the ability of the user to understand the information in the packaging and labeling, such as product labels or instructions for use, that inform the user's actions and that are critical to the safe and effective use of the combination product (e.g., product preparation, administration, maintenance and disposal, or what actions to take if an adverse reaction occurs). Both types of evaluations may be part of the HF Formative and HF Validation studies described below.

    a. *HF Formative Study:* 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. HF Formative studies are iterative and inform the need for user interface changes (e.g., product design or labeling changes) and inform the content of the HF Validation study. For additional information on HF Formative studies see Section III.C.

    HF Validation Study: A study conducted to demonstrate that the final finished combination product user interface can be used by intended users without serious use errors or problems, for the product's intended uses and under the expected use conditions. 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; i.e., the benefit of product use

[14] For combination products that include a device constituent part, design controls must be applied to the combination product. See 21 CFR 4.4; 78 FR 4307 (Jan. 27, 2013). *Current Good Manufacturing Practice Requirements for Combination Products* is accessible at https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products.

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.

2. *Final Finished Combination Product:* The final finished combination product is the product intended for market and submitted in the 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).

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[15]).[16] 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. .

B. Evaluation of Use-Related Risk

Consistent with a risk-based design and development paradigm, the foundation for HF study designs, testing and evaluation should be a use-related risk analysis of a combination product. A use-related risk analysis is a crucial step to help identify use-related hazards associated with the combination product, as well as to characterize high-risk hazards so they can be mitigated or eliminated through improved product interface design. The use-related risk analysis will help identify critical tasks that should be evaluated in a HF study, inform the priority of testing the tasks in a HF study, and determine if there are specific use scenarios to include in testing. A variety of methods can be used to develop and analyze use-related hazards. Two methods frequently used are Failure Mode and Effects Analysis (FMEA) and Fault Tree Analysis (FTA).[17]

The use-related risk analysis should take into account: all the intended uses, users, and use environments; therapeutic or diagnostic procedures associated with the use of the combination product; similar products used within the environments; and any associated medical factors that may affect the safe use of the combination product. In addition, if previous models of the same or similar combination products exist, the risk analysis should incorporate information on known use-related problems with those products. This information can be obtained from the applicant's own experience as well as from public sources such as literature, adverse event reports, and product safety communications.

[15] See CFR 314.126.

[16] The term Major Clinical Study is consistent with other terms such as "phase-3 clinical study," "key clinical study," and "pivotal studies or trials."

[17] For more information on FMEA, FTA and other risk analysis methods, see Guidance for Industry and FDA Staff, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design*, accessible at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationsandGuidance/Guidancedocuments/UCM259760.pdf.

1. Critical Tasks

The use-related risk analysis should identify critical tasks.[18] 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. Thus, categorizing a task as critical is dependent on the unique considerations for each combination product. The Agency expects the risk analysis for the combination product to include an identification of all the critical tasks required for using the combination product, the consequences for failing to perform each critical task correctly, and the strategies that have been applied in the design of the user interface to eliminate or reduce risks to acceptable levels. Such an assessment should include considerations of the indication, the users, the environment and other conditions that might influence the importance of a particular task. Some examples of critical tasks to illustrate this concept include:

- The patient being able to successfully self-administer a drug at the prescribed dose identified in the labeling. Failure to successfully perform this task could harm the patient due to mis-dosing, under-dosing, overdosing, or inability to deliver a dose.
- The user being able to safely dispose of a used syringe. Failure to successfully perform this task could result in needle sticks.
- The patient being able to appropriately navigate the user interface for a patient-controlled analgesia (PCA) delivery system. Failure to successfully perform this task could result in missed doses, inappropriate repeat doses, or overdoses.
- The user being able to understand instructions for inserting a capsule into an inhaler to release the drug, and being able to insert the capsule. Failure to successfully perform this task could result in the patient swallowing the capsule instead of inhaling the contents, lack of treatment effect, or medication related adverse events.
- The user being able to distinguish a product from others of similar appearance. Failure to successfully perform this task could result in delivery of the wrong drug.
- The user being able to complete a series of several critical tasks required to prepare and administer a reconstituted drug from a combination product kit containing a prefilled diluent syringe, drug vial, empty syringe, needle, transfer device and infusion pump. These tasks could include preparing the drug under sterile conditions, connecting the system, and introducing the reconstituted drug solution into an infusion pump. Failure to successfully complete any of these tasks could result in medication errors and/or use-related infection.

Appendix A identifies task failures that may occur with general categories of combination products such as injectors and inhalers. The information can be used to guide the applicant when conducting a risk analysis, which is recommended for any combination product being developed. Additionally, these task failure examples may apply to other types of combination products, and can be used as a reference to help identify and evaluate hazards for other combination products.

[18] For additional information on critical tasks, see Sections 7.3 and 7.4 of *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* at http://www.fda.gov/RegulatoryInformation/Guidances/ucm259748.htm.

2. Intended Users and Use Environments

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). For combination products, distinct user groups generally are health care professionals (HCPs) and lay users (non-health care professionals). Within these two groups there are likely further subgroups based on different tasks, roles, abilities and education. Subgroups of the HCP user population can include those with significantly different roles (e.g., nurses, pharmacists, physicians, emergency medical technicians, home health care providers). 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 with different instructions for use or different hazards. In addition, both the professional role and experience of HCPs can influence interactions with a product. These various differences may justify treating HCPs as distinct user groups that should be evaluated in the HF study as such.

Lay users (non-health care professionals) are those who use the product for self-administration (the patient) or those who administer the product to others as a caregiver (e.g., a family member, sports coach). Within this population, experience of individual users with similar products or products under development may vary widely. For example, when considering a drug-autoinjector combination product, some lay users may be naïve to the use of any autoinjector or may be naïve to the use of certain types of autoinjectors; e.g., those for single dose disposable versus single patient reusable products. Also, lay users may have experience with a different product that might influence their interaction. As a result of these differences, there may be distinct subgroups that should be considered in the use-related risk analysis. As applicable, the HF study should incorporate separate subgroups of lay users.

Environments of use can have diverse characteristics that affect the users' interactions with the product. Thus, the intended environment of use is another important consideration in designing a HF study. Combination products may be used in various professional health care / clinical settings that include emergency departments, intensive care units, inpatient bedsides, procedure suites, outpatient clinics, mobile units, and stocking and storage locations. Likewise, they can also be used in non-clinical settings including homes, schools, offices, and various modes of transportation (e.g., ambulances, airplanes). These environments may vary with respect to temperature, lighting and noise levels, ambient activity levels, number of people in the vicinity, and the availability of associated/accessory medication or devices. Also, a combination product that is intended for home use may be confused with other family member or pet medications stored in the same location. Such environmental conditions may lead to use errors. These environmental factors should be considered in the use-related risk analysis, and included within the design of the HF study as appropriate when they present a use hazard.

3. Training

Training is often proposed as a way to mitigate or control risks. However, before determining if training is appropriate for the combination product, first it is important to eliminate risks that are inherent to the product design. If there are residual risks, the next step is to determine if training

is needed. For example, for a new product that is developed as similar to or an alternative to a currently marketed product with use techniques that are well understood by the users, then training may not be necessary. Such an example might be a prefilled syringe with a staked needle for use by a health care professional. 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.[19]

For combination products when training is expected or needed to control or mitigate residual use-related hazards, it is important to determine what the training is likely to encompass and how it will be performed, who is responsible for conducting the training, and how to ensure consistency in the training method. Consider, for example, a combination product being developed for a hospital-based surgical procedure. A risk analysis might determine that HCP training is required prior to the first use of the product to minimize the risk of errors related to assembling all the combination product constituent parts, preparing the treatment area and the surgical device constituent part before beginning the procedure, administering the drug constituent part(s), monitoring patient responses after using the product, and/or managing interactions across multiple users during the procedure. Due to the nature of the product and its use environment, all users would be expected to receive training before using the product. The HF study would evaluate the adequacy of the training in minimizing these potential risks. In this case, it is likely that FDA would not expect the HF study to evaluate the absence of training.

In addition, when considering training to mitigate residual risks associated with the user interface, it is important to consider how frequently the training will occur, as well as the length of time between the training session(s) and product use. For some combination products, training and first product use is separated by days, weeks, or months. As such, a significant amount of time may elapse between the training session and product use. Retention of information from the first, and possibly the only, training a user receives can decrease over time (i.e., training decay). For example, for a combination product designed for once a week self-injection, post-training information retention one week later can be anticipated to be lower than it would one hour later. 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. The HF Validation study should simulate the effect training decay may have on the users; e.g., simulate the training decay by separating the training and simulated use testing by several hours or days. The protocol should justify the interval to simulate the training decay.

C. Human Factors Formative Studies

HF Formative studies are designed to evaluate early combination product prototypes, taking into consideration the identified use-related hazards. HF Formative study results guide prototype design changes to eliminate or mitigate use-related hazards identified during the product development process. The use of iterative HF Formative studies optimizes the design of the

[19] As appropriate, if user training is necessary, applicants should discuss what methods are appropriate to ensure the provision of training.

combination product user interface for safety, and minimizes the risk of first discovering use problems during late stages of development (e.g., during an HF Validation study, during a major clinical study, or after finalizing commercial plans.).

Iterative HF Formative studies and related design modifications are performed until the user interface design appears to be sufficiently optimized for safety and ready for HF Validation testing. Iterative modifications to the user interface may include changes to the physical design attributes, changes to the packaging and labeling (including instructions for use) and changes to a training program. The results of HF Formative studies should inform the design of the final finished combination product. None of the individual subjects in the HF Formative studies should participate in the HF Validation studies to avoid the potential for bias. For information on HF Knowledge Task studies, see Section III.E; for information on HF Validation studies, see Section III.D below.

D. Human Factors Validation Studies

HF Validation studies demonstrate that the final finished combination product user interface would maximize the likelihood that the product will be safely and effectively used by intended users, for the intended uses in the intended use environments. There are two types of HF Validation studies: HF Simulated-Use and HF Actual-Use Validation. For most combination products, FDA expects that a HF Simulated-Use Validation study will be sufficient to assess the adequacy of the user interface.

1. Human Factors Simulated-Use Validation Studies

The HF Simulated-Use Validation study 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. 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.

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 actual use of the product once introduced into the market. Tasks to be performed in the HF Simulated-Use Validation study should include those critical tasks identified in a use-related risk analysis that may be associated with user interface problems. The study design should provide for the identification of any unanticipated hazards or unexpected use behaviors that were not previously identified.

2. Human Factors Actual-Use Validation Studies

As noted above, FDA expects that for most combination products, a HF Simulated-Use Validation study will be sufficient to assess the adequacy of the user interface design. However, there are rare circumstances when it is difficult to simulate the conditions of use, physical characteristics of the product, or environment of use. Thus, a HF Actual-Use Validation study may be needed to confirm the adequacy of the user interface design.

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 (2) use the final finished combination product in a real (not simulated) environment of use.

- 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. For example, for a drug that causes coughing on inhalation which could result in incomplete dosing, inhaler designs to minimize the risk of not completing an inhalation could not be evaluated without use of the actual drug. This type of assessment using the drug-device combination product would otherwise occur in a simulated-use setting.

- The other type of HF Actual-Use Validation study in a real environment of use. For example, based on the hazard analysis and results of an HF Simulated-Use Validation, it may be appropriate to evaluate in a real environment of use use-related risks associated with a complex combination product intended for use in crisis/emergency settings or with a combination product that has a complex operating procedure. In these instances, the user's tasks could be influenced by the presence of noise, rapidly changing circumstances, distractions, etc. Therefore, the need for a HF Actual-Use Validation study is determined on a case-by-case basis. FDA recommends that applicants for combination products discuss with FDA the availability of simulation techniques and whether HF Simulated-Use Validation and HF Actual-Use Validation studies are needed to evaluate the user interface.[20]

Regardless of the type of HF Validation study, if use errors or problems (e.g., failures, "close calls," use difficulties, and/or new findings) are identified in an HF Validation study, these should be evaluated to (1) identify the root cause(s), (2) determine the potential for harm (including the clinical significance of such errors or problems and the potential for compromised medical treatment), and (3) determine whether additional measures to eliminate or mitigate hazards are necessary. Regardless of the type of HF Validation study, if the HF Validation study shows that additional measures are necessary to address the risk of failures that are deemed clinically significant, then the HF Validation study will be considered failed. Changes to the user interface may be needed to eliminate or mitigate hazards and a new HF Validation study should be performed to evaluate the changes, with the goal of demonstrating that the modifications minimize the risk to acceptable levels without creating additional hazards.

Also, if the product design changes or the user population changes, then the completed HF Validation study may or may not be applicable to the design change. A use-related risk analysis should be completed and, dependent upon the findings of the risk analysis, a new HF Validation study may be advisable to support that the modifications continue to minimize the risk without

[20] 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.

creating additional hazards. If the product design remains unchanged but the applicant seeks to add a new user population, then as applicable, a new use-related risk analysis and new HF Validation study should be performed. See Section V for the relationship of the HF Validation study to the major clinical study.

E. Human Factors Knowledge Task Studies

In situations when the understanding of the information provided in a combination product's labels or labeling is a critical task to using a product safely and effectively, a study to assess the user's understanding of such information (Knowledge Task study) is appropriate. Knowledge Task studies may occur as part of the HF formative, or HF validation process. However, in comparison to other types of HF studies in which critical task performance is assessed by observing user interaction with the product, Knowledge Task studies focus on the understanding and interpretation of important information in the user interface that will be applied to make use-related decisions. The users' understanding of the labeling is evaluated by questioning test participants and assessing whether the information has been understood.

Knowledge Task studies may focus on particular aspects of labeling. For example, a Knowledge Task study could evaluate:

- HCP's understanding of their roles and responsibilities when introducing a combination product as part of a new procedure, or associated with complex medical/surgical procedures that involve many different HCPs;
- The user's ability to select the appropriate task from a lengthy set of instructions that include different options;
- The user's understanding of how to identify defective or expired product;
- The user's awareness and understanding of the combination product's pertinent safety information provided in the instructions for use;
- The user's ability to recognize clinical signs, identified in the instructions for use, that would prompt medical attention; e.g., shortness of breath, allergic reaction, weakness, signs of disease progression; or
- The user's understanding of the diagrams provided in the labeling.

Certain types of Knowledge Task studies are also used in the development of non-prescription products.[21] Generally, these are quantitative studies that evaluate whether results are statistically significant.

IV. PROCESS CONSIDERATIONS

A. Considerations for Submission of Combination Product Human Factors Study Data

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.,

[21] For further information about such studies for non-prescription drug products, see Guidance to Industry *Label Comprehension Studies for Nonprescription Drug Products*, accessible at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm143834.pdf.

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. For example, a syringe is not on the list of high priority devices for human factors review, and the following illustrates certain considerations for when a HF Validation study may be needed for a prefilled syringe.

- A prefilled syringe with a staked needle and needle guard for use by HCPs in an acute care setting:
    - If the syringe, needle and needle guard design is commonly used and well understood (absent other use-related risk concerns for the combination product as a whole), FDA would not expect a HF Validation study for such products. 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.
    - If the syringe, needle and needle guard are of a unique/novel design, there are use experience concerns with similar products, or there are other factors that increase the use-related hazard, then an HF Validation study should be conducted.

- The same prefilled syringe with needle guard for use by patients with neuromuscular disorder or visual impairment:
    - Because the user characteristics and associated medical symptoms present unique user profiles that may affect safe use of the product, an HF Validation study should be conducted to demonstrate that the product design adequately mitigates the risks for its intended use in these patients, and use environments.

- The same prefilled syringe with needle guard and a unique application of color to distinguish it from different drugs in similar prefilled syringes to help prevent medication errors:
    - Even if factors such as indications for use, intended users, and use environment remain unchanged, based on the use-related risk analysis, an HF Validation study may be necessary to ensure that HCPs can readily distinguish the new syringe from similar prefilled syringes containing different drugs. As appropriate, such a study might focus on knowledge-based tasks.

- The same prefilled syringe with needle guard that is used with various tubing, connectors, pumps and other device components in a high risk procedural setting:
    - A HF Validation study is likely necessary to assess the entire system. As applicable, the HF Validation study may include detailed assessments of the instructions, diagrams, training or other aspects that might become part of a postmarket safety program.

Other scenarios and alternative approaches are possible. As with all product development, FDA encourages applicants to contact the Agency to discuss the specific product proposals.

B. Considerations for Design Changes After HF Validation

FDA recognizes that combination product design changes may occur premarket or postmarket after HF Validation studies have been completed. For example, during premarket development the results of a clinical trial may reveal design flaws that were not detected in HF Formative or HF Validation studies. 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.

Some modifications to a product's internal design or to some of its external features may not need validation in a HF study (e.g., a change in a material that does not affect user interface). 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.

When making design changes, the applicant should conduct an updated use-related risk assessment of the new design. FDA encourages applicants to follow the HF principles outlined in this document. Conceptually, this analysis should consider such things as:

- 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 an existing critical task or add a new critical task?
- Does the design change alter the expected users or their knowledge base?

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.

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 change.[22] (Also, see Section IV.A for further information that may be useful in considering the HF implications of a design change.)

C. Review of Human Factors Information in Combination Product Investigational Applications

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

[22] The use of other types (i.e., non-HF) of studies (e.g., clinical, pharmacokinetic, or non-clinical studies) to evaluate combination product design changes is beyond the scope of this document.

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 use-related risk analysis indicates that a HF study is necessary, FDA encourages applicants to submit the following HF information for feedback before commencing the HF Validation study:

- Use-related risk analysis and any updated risk analysis of design changes;
- A summary of HF Formative study results and analysis;
- A summary of changes made to the product user interface after the HF Formative studies, including how the results from the HF Formative studies were used to update the user interface and use-related risk analysis;
- The draft HF Validation study protocol; and
- Intend-to-market labels and labeling (including instructions for use if any are proposed) that will be tested in the HF Validation study.

When this information is submitted to the investigational application, FDA will review the information, including the use-related risk analysis and the draft HF Validation study protocol, and intends to provide comments or recommendations to increase the likelihood of an acceptable HF study design that will adequately test for potential use failures. Also, during Agency review of draft HF Validation study protocols that include product labeling (e.g., instructions for use), FDA intends to provide preliminary comments on the user interface labels and labeling being However, final labeling is determined after review of the entire marketing application that includes information beyond that in the HF Validation study.

D. Review of HF Studies and Certain Labeling in Marketing Applications

As applicable, FDA will review HF Validation study results submitted in the marketing application to assess whether the data confirm validation of the user interface and certain aspects of the proposed labels and labeling (e.g., instructions for use). FDA cautions applicants leveraging a master file for HF data, that in some instances the master file data may suffice for one constituent part alone, but not for the combination product as a whole (e.g., device with a specific drug/biological product). The applicant should determine whether sufficient information would be available in the master file or whether the applicant should conduct and submit additional HF studies for the combination product as a whole.

During FDA review of labeling[23] in a marketing application, FDA may determine that the final user interface labeling should differ from the HF Validated labeling. This may occur, for example, based on the results of the major clinical trial, other safety data or medication error data, new nomenclature considerations, and labeling content and format requirements. The labeling assessment also considers current postmarket experience with the same or similar products, which might indicate that modification of the instructions for use is appropriate to mitigate a risk. After review of the marketing application, depending on the potential impact of resulting labeling differences on performance of critical tasks, an additional HF Validation study

[23] Labeling review includes consideration of labeling claims that might be provided by a HF study (e.g., user preference or ease of use) and whether the data support those claims.

may be needed to ensure that the changes minimize the use-related risks without creating additional hazards.

V. RELATIONSHIP OF HUMAN FACTORS AND MAJOR CLINICAL STUDIES OF THE COMBINATION PRODUCT

As explained in preceding sections of this document, HF studies of a combination product are conducted as part of the product design controls process. An appropriate HF development program will maximize the likelihood that the combination product user interface is safe and effective for use by the intended users, uses and use environments. However, the HF Validation study is not sufficient to establish the safety and effectiveness 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 effective use of the product.[24]

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.

FDA recognizes that in some circumstances the data to support safety and efficacy of the combination product may adequate without the inclusion of the final finished combination in a major clinical trial. For certain products, the sequencing of the HF study prior to the clinical study may be less critical to inform our understanding of the product's safety and efficacy, allowing for greater flexibility in the timing of the human factors validation study relative to a major clinical studies. In other cases, a sponsor may encounter a need to change the combination product design in the course of the development program, even after clinical studies have been completed. The type and extent of data to support such changes depend on the nature of change, development stage, and other contextual factors, and FDA would consider the totality of the data provided to support the approvability of the combination product in any such circumstances. However, for certain combination products, we might expect or encourage you to use the final finished combination product in your major clinical studies. In such cases, we recommend that you conduct the HF-Validation study on the final finished combination product prior to the major clinical studies.

And, in all cases, we encourage you to discuss your combination product development plans with the Agency as appropriate and consider such discussion as a component of your development meeting, including the pre-IND, IDE and EOP2 meetings

[24] See 21CFR 201.56(a)(1).

VI. HOW TO OBTAIN ADDITIONAL INFORMATION

FDA encourages applicants to request early discussions with FDA regarding their HF program and the type of HF studies that might be appropriate or necessary in the planned submission. Additionally, if applicants anticipate design changes during product development before launch, FDA strongly encourages meetings during the early planning stages. Discussion topics might include how to add a new configuration to the development plan and/or how to bridge to existing data. Such discussions should provide clarity on the applicant's development plan and provide transparency on FDA recommendations and expectations on HF studies and sequence of the development program. Where appropriate, the applicant may request focused meetings for more detailed discussions. For a combination product, applicants should submit meeting requests to the lead center using the process and procedures of the lead center. The meeting request should indicate that the discussion is for a combination product and request participation of all relevant centers and Office of Combination Products as appropriate. Additional information on requesting meetings is provided in the last two guidance documents listed below.

The following FDA documents may be useful:

- Guidance for Industry and FDA Staff – Applying Human Factors and Usability Engineering to Optimize Medical Device Design; http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm
- Draft Guidance for Industry – Safety Considerations for Product Design to Minimize Medication Errors; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf
- Draft Guidance for Industry – Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf
- Guidance for Industry – Label Comprehension Studies for Nonprescription Drug Products; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm143834.pdf
- Draft Guidance for Industry – Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm184128.pdf
- Guidance for Industry – Formal Meetings Between FDA and Sponsors or Applicants; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm153222.pdf
- Guidance for Industry and FDA Staff – Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff; http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf

APPENDIX A: USER TASK FAILURE EXAMPLES

Table 1 and Table 2 below provide examples of some user task failures that typically apply to injection and inhalation combination products. Table 1 applies to combination products with injectors (e.g., pen injectors, autoinjectors, prefilled syringes), and Table 2 applies to combination products with certain inhalation systems (e.g., nebulizers and inhalers).

In addition to the examples in these tables, there may be knowledge tasks that require user understanding of information that is not typically or easily evaluated through observation of simulated use. Knowledge tasks are derived from the product labeling (including user manual, Medication Guide, labels on the device itself) and training package.

The tables do not present comprehensive all-inclusive lists. If the combination product requires users to perform tasks not contained in the tables that could result in harm if not performed correctly, then those tasks should be included in the HF Validation study. Also, depending upon the product design, only certain tasks may be applicable to a specific combination product. The critical tasks may change depending on the indications, use environments, user populations that have unique or novel risks, and other characteristics and features of the combination product. Therefore, a use-related risk analysis should be performed before identifying tasks for evaluation in a HF Validation study. Once identified, those tasks should be used to construct the HF Validation study.

(Intentionally blank)

693

Table 1: Examples of Critical Tasks for Combination Products that Deliver Dose by Injection		
User Task	**Possible Task Failures and Use Errors**	**Possible Hazard / Harm Resulting from Failures/Use Errors**
Understand how to dose the product	▪ Misunderstanding dosing instructions ▪ Not aware of dosing instructions	▪ Overdosing ▪ Under dosing ▪ Missed dose
Understand how to administer the product	▪ Improper technique while interacting with the product during dosing ▪ Cannot complete injection	▪ Overdosing ▪ Under dosing ▪ Missed dose ▪ Needlestick injury ▪ Accidental exposure to others
Product differentiation	▪ Select incorrect product	▪ Wrong drug delivered
Open packaging	▪ Damage to device ▪ Loss of instructions or components ▪ Inability to open package	▪ Delay of therapy ▪ Missed dose ▪ Over or under dosing ▪ User injury
Evaluate device and drug prior to dosing	▪ Failure to check injector window for drug condition ▪ Expired or adulterated drug used ▪ Use device that is not functional for dose delivery ▪ Use damaged needle	▪ Painful injection ▪ Reduced drug efficacy ▪ Delay of therapy ▪ Missed dose ▪ Infection
Prepare injection site	▪ Not cleaning/disinfecting injection site	▪ Infection
Prepare/mix the dose for injection	▪ Mix or Measure the product incorrectly ▪ Wrong drug amount drawn into the syringe	▪ Reduced drug efficacy ▪ Under dosing ▪ Overdosing
Prime injector/syringe for injection.	▪ Not priming at all or priming incorrectly	▪ Inaccurate dosing ▪ Under dosing
Select injection site	▪ Identify incorrect injection site	▪ Painful injection ▪ Lack of drug efficacy ▪ Local or systemic adverse events
Remove syringe needle cover	▪ Do not remove needle cover or injector cap	▪ Missed dose ▪ Delay of therapy
Attach needle	▪ Do not attach needle	▪ Missed dose ▪ Delay of therapy
Remove injector cap	▪ Do not remove injector cap	▪ Missed dose ▪ Delay of therapy
Hold injector/syringe in correct orientation	▪ Hold injector/syringe incorrectly ▪ Inject upside down	▪ Needle stick injuries ▪ Delay of therapy ▪ Reduced drug efficacy
Depress syringe plunger/ activate autoinjector (press injection button)	▪ Unable to depress the plunger ▪ Unable to activate injector fully ▪ Unable to determine if dose delivered	▪ No dose ▪ Under dosing
Hold syringe or injector at injection site	▪ Premature removal of syringe/injector ▪ Wet injection (drug solution on surface of injection site)	▪ Under dosing ▪ Missed dose
Verify dose delivery	▪ Not verifying complete dose delivery	▪ Under dosing ▪ Missed dose
Dispose/clean/store syringe/injector	▪ Improper disposal/storage ▪ Inject degraded product ▪ Do not clean reusable device	▪ Needle stick injuries ▪ Contamination /transmission of disease (infection) ▪ Reduced drug efficacy ▪ Delay of therapy ▪ Drug diversion ▪ Exposure of non-users

694

Table 2: Examples of Critical Tasks for Combination Products that Deliver Dose by Inhalation		
User Task	**Possible Task Failures and Use Errors**	**Possible Hazard / Harm Resulting from Failures/Use Errors**
Understand how to administer the product	▪ Improper technique while using the product during dosing ▪ Cannot complete inhalation	▪ Overdosing ▪ Under dose ▪ Missed dose ▪ Accidental exposure to others
Understand how to dose the product	▪ Misunderstanding dosing instructions ▪ Not aware of dosing instructions	▪ Overdosing ▪ Under dosing ▪ Missed dose
Open packaging	▪ Damage to device ▪ Loss of instructions or components ▪ Inability to open package	▪ Delay of therapy ▪ Missed dose ▪ Wrong dose ▪ User injury
Assemble product	▪ Assembled incorrectly ▪ Unable to assemble	▪ Choking on device components ▪ Delay of therapy ▪ Missed dose or dosing error
Evaluate device and drug prior to dosing	▪ Expired or adulterated drug used ▪ Use device that is not functional for dose delivery ▪ Use damaged product	▪ Reduced drug efficacy ▪ Delay of therapy ▪ Missed dose or dosing error
Set up dose; prime product	▪ Not preparing dose for inhalation ▪ Not priming at all or priming incorrectly	▪ Under dosing or overdosing ▪ Choking on dose capsule (if present) ▪ Missed dose
Use device to deliver dose	▪ Improper inhalation technique ▪ Improper seal of mouth on mouthpiece	▪ Under dosing or over-dosing ▪ Missed dose or dosing error ▪ Coughing
Waiting a specific amount of time between doses for multiple breath dosing	▪ Not waiting long enough between doses	▪ Under dose ▪ Lack of efficacy
Disassemble, maintain, store, and clean reusable device components	▪ Failing to clean or maintain. ▪ Storing at wrong temperature or under other incorrect conditions	▪ Delay of therapy ▪ Under dosing or overdosing ▪ Infection ▪ Reduced drug efficacy
Dispose of device as per instructions.	▪ Failing to properly dispose of device	▪ Diversion of drug ▪ Exposure to non-users

695