ANALYSIS

Draft Guidance for Industry and FDA Staff: Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development

When finalized this guidance will represent FDA's current thinking on Human Factors (HF) studies and data to needed validate the design of a device-containing combination product to support investigational exemption and marketing applications. The draft guideline discusses different types of design validation studies (i.e., simulated use, actual use and knowledge based assessments), and their timing/sequencing, that are conducted during product development, and in support of design changes. It also explains how HF studies relate to clinical studies. Much of what is discussed in the draft guidance is also covered in other FDA guidance documents for medical devices (e.g., Final Guidance: Applying Human Factors and Usability Engineering to Medical Devices). The following summary highlights points covered in the draft guidance that are specific to combination products.

Advice on HF Studies

- HF studies of drugs intended for self-administration should assess the ability of users to properly prepare and administer the drug at the labeled/prescribed dose and avoid mis-dosing, under-dosing, overdosing, or inability to deliver a dose, and assure safe disposal. Users should be able to distinguish the product from others of similar appearance.
- For drugs administered by infusion pump, users should be able to complete the critical tasks required to prepare the drug, transfer it to reconstitution and delivery devices, and connect the delivery device to the infusion pump.
- Differences between lay users (patient/caregiver) and healthcare professionals (HCP) experience may justify treating health care providers as a distinct user group(s).
- If a combination product intended for home use may be confused with other family member or pet medications stored in the same location, these environmental factors should be considered in the risk analysis and included in the design of the design validation study.

- When training is expected/needed to control or mitigate residual use-related hazards, it is important to determine what the training will encompass, how it will be performed, who is responsible for its conduct, and how to ensure consistency. Training may not be necessary for a new product intended to be similar, or as an alternative, to a currently marketed product, when use techniques are well understood by users (e.g., a prefilled syringe with a staked needle for use by a health care professional). If there are residual risks for which training may be an appropriate hazard mitigation, consider if training will occur routinely/consistently before first use. Where training would be appropriate but is not expected to routinely/consistently occur, HF studies should evaluate the user interface in the absence of training. The HF design validation study should simulate the effect training decay. Consider how frequently the training will occur, as well as the length of time between the training session(s) and product use. 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 protocol should justify the interval to simulate the training decay.

Simulated-Use, Actual Use and Knowledge Assessment Studies

- For most combination products, a HF simulated-use validation study will be sufficient. 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. Simulation methods vary and may include the use of a manikin, injection pads, placebo, and other elements intended to simulate the patient, the procedure and the use environment.
- There may be circumstances where it is difficult to simulate the conditions, physical characteristics of the product, or environment of use. In these circumstances an actual-use design validation study may be necessary. Actual-use studies involve the final finished combination product (including drug, not placebo) in a simulated use setting, or the use of the final finished combination product in a real (not simulated) use environment. A HF actual-use design validation study of a 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. The draft guidance recommends that combination product applicants discuss with FDA the availability of simulation techniques and whether HF simulated-use design

validation and HF actual-use design validation studies are needed to evaluate the user interface.

- In situations where understanding of the information provided in a combination product labeling is critical to using a product safely and effectively then conducting a study to assess user understanding of such information is appropriate. Knowledge assessments may occur as part of formative HF and/or summative HF validation studies. Knowledge assessments focus on the understanding and interpretation of user interface information that will be applied in making use-related decisions. They differ from other types of HF studies where critical task performance is assessed by observation. Some of the critical tasks that may be evaluated in a knowledge assessment are: identification of defective/expired product, awareness/understanding of pertinent safety information in the instructions for use, recognition of clinical signs identified in the instructions for use that prompt medical attention and understanding labeling diagrams.

HF Information in Applications

- HF data and/or a risk assessment should be submitted for 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 for combination products having a device constituent part for which FDA has indicated that human factors data should be submitted (see Draft Guidance for Industry and Food and Drug Administration Staff: List of Highest Priority Devices for Human Factors Review). If the risk assessment identifies the need for HF studies, then a HF design validation study should be conducted and the results submitted to FDA. In general, a HF design validation study may not be necessary for a prefilled syringe with a staked needle and needle guard which is intended for professional use in an acute care setting if the design is commonly used and well understood by HCPs. If the syringe, needle or needle guard are of a unique/novel design, or if there are use experience concerns with similar products, or there are other factors that increase use-related hazard(s), then an HF design validation study should be conducted. Even if factors such as indications for use, intended users, and use environment remain unchanged, based on the use-related risk analysis, an HF design validation study may be necessary to ensure that HCPs can readily distinguish the new syringe from similar prefilled syringes containing different drugs. The same prefilled syringe with needle guard used by patients with neuromuscular disorder or visual impairment

for self-administration would require a HF design validation study as would the unique application of color to distinguish a particular syringe from another. For a prefilled syringe used with tubing, connectors, pumps and other device components in a high risk procedural setting, a HF design validation study of the entire system is likely to be needed. FDA encourages applicants to contact the Agency to discuss specific product proposals.

- A risk analysis should be submitted in the investigational exemption application for a combination product. If the applicant determines from the risk analysis that a HF study is not needed, this should be justified and the supporting risk assessment should be provided. If the risk assessment indicates a HF study is necessary, FDA encourages applicants to submit the following HF information for feedback before commencing the HF design validation study:
    - Use-related risk analysis and any updated risk analysis of design changes
    - Summary of HF formative study results and analysis
    - Summary of changes made to the product user interface after HF formative studies, including how the results from the HF formative studies were used to improve the user interface
    - Draft HF design validation study protocol
    - Draft labels and labeling (i.e., instructions for use, training materials) to be tested in the HF design validation study.
- FDA intends to provide preliminary comments on the user interface labels and labeling following its review of draft HF design validation study protocols and product labeling. Final labeling is determined after review of the entire marketing application including information beyond that in the HF design validation study.
- FDA cautions applicants leveraging a master file containing HF data. In some instances, master file HF data may suffice for one constituent part alone, but not for a combination product as a whole (i.e., device with a specific drug/biological product). The applicant should determine if sufficient information is available in a particular master file and if it is necessary to conduct and submit additional HF studies for the combination product as a whole.
- Depending on the outcome of its review, final approved labeling may differ from HF validated labeling. Depending on the potential impact of final labeling changes, an additional HF design validation study may be needed to ensure that the changes minimize the use-related risks without creating additional hazards.

HF Relationship to Clinical Studies

- Before conducting major clinical study(ies), a HF design validation study should be conducted on the finished combination product and labeling. The HF validated product would then be ready for further evaluation in major clinical study(ies) to be submitted in the marketing application. In some cases, it may be appropriate to conduct HF studies in parallel or after the completion of major clinical studies in order to assess design modifications.
- In some circumstances, data to support safety and efficacy of the combination product may be adequate without the inclusion of the final finished combination in a major clinical study. In some cases, sequencing of the HF study prior to the clinical study may be less critical to informing 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. Under other circumstances, it may be necessary to change the combination product design during the course of development even after clinical studies have been completed. The type and extent of data to support such changes depends 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. For certain combination products, FDA might expect or encourage the use of the final finished combination product in major clinical studies. In such cases, the HF design validation study should be conducted on the final finished combination product prior to initiating major clinical studies.

Design Changes

- 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 design 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 design validation study assessments. If the product design changes or the user population changes, then completed HF design validation studies may no longer be applicable, following the design change. Following design change, depending on the findings of a risk assessment, a new HF design validation study may be needed to show that the modifications continue to minimize the risk and do not create new hazards.

- If the product design remains unchanged but an additional the user population is being sought then, as applicable a new use-related risk analysis and new HF design validation study should be performed. A HF design validation study is appropriate if clinical studies reveal design flaws that were not detected in HF formative or HF design validation studies. Or, during post-market development, design changes to the marketed combination product may be implemented to respond to use-related safety reports, complaints/problems, to address a manufacturer-initiated post-market corrective and preventative actions, or to meet the needs of an expanded indication or user population. When contemplating design changes, an updated use-related risk assessment should be conducted to assess amongst other things changes to the design of the user interface, critical tasks, and user knowledge.
- FDA encourages the applicants to discuss with the Agency plans for managing change and the types of HF and other clinical or non-clinical studies that may be needed to support approval of the change. To facilitate discussion, where needed the applicant should provide a proposal for additional HF testing to support a design change. The proposal should include a detailed description of why the change is being made and what 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.

Commentary:

- *The draft guidance provides needed insights into what FDA thinks it thinks about human factors studies for combination products. Industry comments should be submitted by May 3, 2016 to http://www.regulations.gov.*
- *There is little in this guidance that should provoke strong reactions from industry, except for FDA recommendations on the timing and sequencing of design validation studies and how this relates to clinical studies.*
- *Some of the approaches stated in the draft guidance are likely to be generalizable.*
- *The problem with FDA human factors review is the timing of Agency feed-back on protocols and labeling. Delays in FDA responses can extend critical development timelines. Labeling changes, in particular to Instructions for Use, when they come after the completion of design validation studies, are likely to result in the need to repeat design validation.*