Chimera Consulting: Combination Product Training Institute®

US FDA ISSUES GUIDANCE ON HUMAN FACTORS STUDIES FOR COMBINATION PRODUCTS

This is the second in a series of articles covering quality system requirements for combination products and borderline products in the US and EU. In February 2016, the US FDA issued three guidance documents which focus on identifying, assessing and mitigating hazards related to how people use medical products that include a medical device. In this Article, Adam Shames, MBA, Chief Executive Officer, Core Human Factors, and Michael Gross, PhD, RAC, Principal Consultant, Chimera Consulting® and Head, Combination Product Training Institute®, summarise the FDA's recently released draft Guidance: "Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development".

USE-RELATED HAZARDS

Combination product users, such as patients, professional and lay caregivers, pharmacists and physicians have unique needs that vary from product to product, but all users need all products to be safe and effective. Human factors engineering (HFE) and usability engineering (UE) provide the necessary tools to identify, assess and mitigate use-related hazards. According to the US FDA, the "goal is to...eliminate or reduce to the extent possible" anything related to the user-device interface "that could cause harm or degrade medical treatment". In particular: "Drug development should take into account the user interface and factors that can reduce the risk [of] medication errors, i.e. features to enhance patient safety." Note that "the user interface includes all points of interaction between the product and the user(s) including elements such as displays, controls, packaging, product labels, and instructions for use".

The HFE/UE "processes can [also] be beneficial for optimising user interfaces in other respects (e.g. maximising ease of use, efficiency, and user satisfaction)" but FDA is "primarily concerned that device-containing medical products are safe and effective for the intended users, uses, and use environments", and the guidance is focused on that singular goal. Therefore, manufacturers interested in other uses of HFE/UE besides risk control should look elsewhere. Some recommended guidance documents for those other goals are ANSI/AAMI HE75[1] and ANSI/AAMI/IEC 62366-1.[2]

FDA GUIDANCE & DRAFT GUIDANCE

On February 3rd, 2016 the FDA issued three guidance documents describing how they expect industry to address use-related hazards as part of their overall risk-management process. The first document came from the Center for Devices and Radiological Health (CDRH) and is the final version of a draft that was published back in 2011. It is titled: "*Applying Human Factors and Usability Engineering to Medical Devices: Guidance for Industry and Food and Drug Administration Staff*".[3] The second document also came from CDRH and is a draft titled: "*List of Highest Priority Devices for Human Factors Review*".[4] The third document came from the Office of

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Combination Products (OCP) and is also a draft, entitled: "*Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development: Draft Guidance for Industry and FDA Staff*".[5]

Together, these guidances provide insight into how the FDA views the risks associated with use-related hazards and their expectations for how manufacturers should follow HFE/UE processes during the development of combination products.

HUMAN FACTORS & USABILITY ENGINEERING

The HFE/UE process can start at any time. However, "user interface design flaws identified during formative evaluation [i.e. early, information-gathering human factors studies] can be addressed more easily and less expensively than they could be later in the design process". The process is started and scaled appropriately when it is done in relation to the potential for harm as a result of use-related hazards. A typical HFE/UE process includes three steps, which the FDA calls "essential". They are:

1. The identification of use-related hazards
2. The elimination or mitigation of those hazards (i.e. the control of the hazards)
3. Demonstration that the hazards have been successfully & sufficiently controlled.

Whilst each product should have a process tailored to its unique characteristics, successful HFE/UE processes conclude with the same statement that the product "has been found to be safe and effective for the intended users, uses, and use environments".

USE-RELATED HAZARDS UNIQUE TO DRUG DELIVERY SYSTEMS

Drug delivery device use typically exposes users, particularly those self-administering, to at least the following hazards: overdose, under-dose, missed dose, inadvertent needle-sticks (when a needle is involved) and transmission of blood-borne pathogen (when a needle or other sharp is involved). Therefore, users of combination products which are intended for drug delivery must be able to prepare properly and administer the drug safely at the labelled/prescribed dose and assure correct disposal. Also, users must be able to distinguish the product from others of similar appearance such as when medication for other conditions and for "other family member or pets" is "stored in the same location".

USERS

Professional caregivers (such as nurses and physicians), lay caregivers (friends and family), and patients are all exposed to the use-related hazards associated with combination products. According to the FDA, a determination of user groups examines whether use-related hazards that may affect two or more people can be analysed, controlled and evaluated in the same manner. If there are "meaningful differences in capabilities or use responsibilities between user populations that could affect their interactions with the device (such as lay and professional users who might use the same device to perform different tasks or different types of professionals who might perform different tasks on the device)", then there are different,

unique user groups. Further, for combination products, users may be grouped as nurses, pharmacists, physicians, emergency medical technicians, home health care providers, lay caregivers and self-administering patients. In addition, since a user's experience may affect how they use a product, it may be necessary to include groups of users with and without "experience of similar-appearing products with different instructions for use or different hazards".

Training is only appropriate as a last resort to control a use-related hazard. If training is necessary to control a use-related hazard, FDA says: "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 "whether there is an expectation that training will routinely and consistently occur, before the first use of the combination product".

"Together, these guidances provide insight into how the FDA views the risks associated with use-related hazards and their expectations for how manufacturers should follow HFE/UE processes during the development of combination products."

USING TRAINING TO CONTROL USE-RELATED HAZARDS

The following controls are in order of priority: 1) inherent safety by design; 2) protective measures; and 3) information for safety (including training). How FDA prioritises the use of these controls to mitigate design flaws is clear in the guidance and is consistent with established international standards such as ANSI/AAMI/ISO 14971.[6]

When training "is not expected to routinely or consistently occur", human factors testing "should evaluate the user interface in the absence of training". When training is included in human factors testing, the testing "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 specific interval of decay should be justified in the study protocol and training materials.

ABOUT THE AUTHORS

Adam Shames is a recognised human factors expert and consultant and is the Founder and Chief Executive Officer of Core Human Factors, Inc, a leader in human factors and usability engineering consulting services with over 12 full-time employees. Adam holds an MBA in international business and a BS in human factors engineering and psychology. He received the De-Florez Prize in Human Engineering and holds a Certificate in Applied Ergonomics Training from the United States Army Center for Health Promotion and Preventive Medicine. Adam has over 15 years of human factors research experience and has served as the Principal Investigator on hundreds of IRB reviewed usability studies involving thousands of participants in cities around the world.

Michael Gross is the Principal Consultant of Chimera Consulting®, specialising in quality assurance, regulatory affairs and technical development of drugs, biologics, medical devices and combination products. He also heads the Combination Product Training Institute®, which provides professional training programs on combination product topics. Michael holds a PhD in Organic Chemistry and conducted post-doctoral research in biochemistry at the National Institutes of Health. He is a former FDA reviewer and inspector. Michael worked for 30 years in senior quality, compliance and regulatory affairs roles for a number of large and small pharmaceutical and medical device companies. Today, he provides an influential industrial perspective on the regulation of combination products and is a frequent speaker on combination products topics and has published numerous articles in regulatory and scientific publications.

HUMAN FACTORS STUDIES & CLINICAL STUDIES

According to the draft guidance, the human factors validation study (which is the study intended to "demonstrate that the final finished combination product user interface would maximise the likelihood that the product will be safely and effectively used by intended users, for the intended uses in the intended use environments") should ideally occur before conducting major clinical studies (i.e. studies intended to "provide the primary support for the safety and effectiveness of a product for a proposed indication").

If the final finished combination product will be used in major clinical studies, the human factors validation should be conducted on the final finished combination product prior to initiating major clinical studies. However, FDA acknowledges that the "sequencing of the human factors study prior to the clinical study may be less critical to inform our understanding of the product's safety and efficacy".

Further, "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".

While these studies can be conducted sequentially or in parallel, it is nearly impossible to conduct one study to support both objectives. This is due to the fundamental nature of most of these studies – that they are controlled studies in which independent variables are controlled and dependent variables are not controlled. In clinical studies, use of the combination product is typically one of the independent variables that needs to be controlled and this is the exact opposite in human factors studies in which use of the combination products is the dependent variable and is therefore not controlled. Use in a human factors study should not be controlled because use of the combination product is specifically what is intended to be evaluated.

SIMULATED VS ACTUAL USE

Most combination products should be evaluated in a simulated use study but there are some instances in which simulated use is insufficient to assess all aspects of safety and effectiveness. OCP proposes that there are two types of human factors validation studies: 1) simulated use, and 2) actual use. They further divide actual use studies

into two subcategories: 2a) actual use in a simulated environment, and 2b) actual use in a real environment.

When simulated, the simulation should be sufficiently realistic so that the results of the study are representative of aspects of actual use of the product once introduced to the market. OCP states that "there are rare circumstances when it is difficult to simulate the conditions or use, physical characteristics of the product, or environment of use", and it is therefore necessary to conduct an actual use study.

LABELS & LABELLING

"In situations where the understanding of information provided in a combination product's labels or labelling 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," says FDA. 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 human factors 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 labelling diagrams.

SUBMITTING HUMAN FACTORS INFORMATION TO FDA

A use-related risk analysis "should [always] be submitted in an investigation application", since a "combination product's specific use-related risk analysis generally informs the Agency's expectations" for whether additional human factors data should also be submitted. In general, additional human factors data should be submitted to the FDA as part of the application whenever there is potential for serious harm resulting from use error or whenever the FDA specifically requests it either through device specific guidance or while in consultation with an applicant. The FDA encourages applicants to contact them to discuss specific product proposals.

However, regardless of whether additional human factors data must be submitted as part of the application, FDA expects that all applicants are compliant with 21 CFR 820.30 – Design Controls, which mandates the conduct and documentation of human factors activities throughout the design and development process.

The "FDA encourages applicants to submit the following human factors information for feedback before commencing the HF Validation study:

1. Use-related risk analysis and any updated risk analysis of design changes
2. A summary of human factors formative study results and analysis
3. A summary of changes made to the product user interface after the formative studies, including how the results from those studies were used to update the user interface and use-related risk analysis
4. The draft human factors validation study protocol
5. Intend-to-market labels and labelling (including instructions for use if any are proposed) that will be tested in the human factors validation study.

The FDA states that it "intends to provide preliminary comments on the user interface labels and labelling. However, final labelling is determined after review of the entire marketing application that includes information beyond that in the human factors validation study". Depending on the outcome of its review, final approved labelling may differ from what is tested in the human factors validation study. Therefore, "an additional human factors validation study may be needed to ensure that the labelling changes minimise the use-related risks without creating additional hazards".

CONCLUSION

HFE/UE is a time-proven method for reducing use-related hazards. If products are not developed with awareness and implementation of HFE/UE controls, end-users will be more likely to injure themselves, or fail to receive needed medical treatment. This is why the FDA, which is responsible for regulating safety and effectiveness of drugs, biologics and medical devices, including combination products, has issued these new guidances to explain its current thinking on what actions are necessary during the development and post-market approval management of new products.

Please visit the Chimera Consulting® website (www.ChimeraConsultingNA.com) for additional analysis of the draft guidance.

REFERENCES

1. *ANSI/AAMI HE75:2009/(R)2013 Human factors engineering – Design of medical devices.*
2. *ANSI/AAMI/IEC 62366-1:2015 Medical devices – Part 1: Application of usability engineering to medical devices.*
3. *Applying Human Factors and Usability Engineering to Medical Devices: Guidance for Industry and FDA Staff.*
4. *List of Highest Priority Devices for Human Factors Review.*
5. *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development: Draft Guidance for Industry and FDA Staff.*
6. *ANSI/AAMI/ISO 14971:2007/(R)2010 Medical devices – Application of risk management to medical devices.*

THE COMBINATION PRODUCT TRAINING INSTITUTE

In 2016, the Combination Product Training Institute® will conduct two identical three-day training programs that address quality system and design controls requirements for combination and borderline products in the US and EU, and the conduct of human factors studies. These programs will cover requirements for both newly developed and legacy products as well as quality system obligations of device component manufacturers. The first of the two training programs will take place on March 29-31, 2016 at the Chemical Heritage Foundation Conference Center (Philadelphia, PA, US). The second program will take place on June 14-16, 2016 at the NH Barbizon Palace (Amsterdam, The Netherlands).

Throughout the year, the Combination Product Training Institute will offer other venue-based training programs on various combination product topics. In-house training programs are also available. For additional details please visit the Combination Product Training Institute website at: CombinationProductTrainingInstitute.com