Use-Related Risk Analysis (URRA) and Human Factors (HF) Protocol Reviews: What to Submit for an Efficient Review

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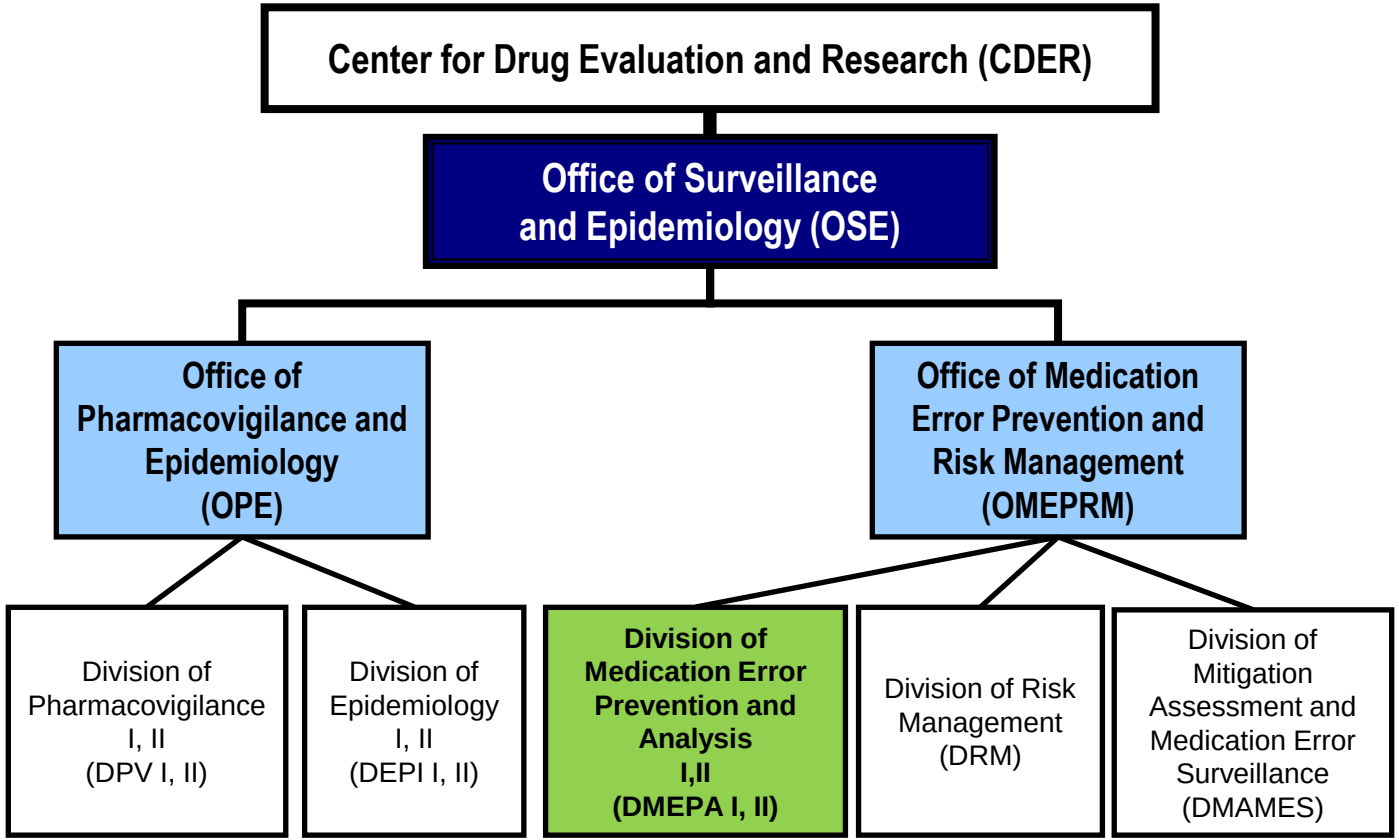
Learning Objectives

- Define the objectives of a Use Related Risk Analysis (URRA)
- Define the objectives of a Human Factors (HF) validation study protocol
- Describe the Biosimilar User Fee Amendments (BsUFA) III/Prescription Drug User Fee Amendments (PDUFA) VII Commitments related to HF submissions
- Describe common Agency initiated information requests for HF submissions
- Identify tips which may result in a more efficient Agency review of URRA and HF validation study protocol submissions
- Discuss the importance of the early identification of HF data needs for medical product development


Center for Drug Evaluation and Research (CDER)
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Division of Pharmacovigilance I, II (DPV I, II)
Division of Epidemiology I, II (DEPI I, II)
Division of Medication Error Prevention and Analysis I,II (DMEPA I, II)
Division of Risk Management (DRM)
Division of Mitigation Assessment and Medication Error Surveillance (DMAMES)

DMEPA's Mission

To increase the safe use of drug products by minimizing **use error** that is related to the naming, labeling, packaging, or design of drug products


Proprietary Names
Labels/ Labeling/ Packaging/ Product Design
Human Factors
Post-market Surveillance/ signals
Guidance/ Policy/Other
DMEPA Mission

Who Looks at Medication Errors?

Divisions of Medication Error Prevention and Analysis (DMEPA I and DMEPA II)

- Created in 1999
- Healthcare professionals, scientists and engineers with varied professional backgrounds
- Divided by therapeutic categories into DMEPA I & DMEPA II
- Leads CDER review pertaining to **medication error prevention and analysis and human factors** for drug and therapeutic biologics

HF Evaluation of Drug, Biologic, and Combination Products in CDER/CBER

- Evaluate HF submissions for drugs, biologics, and combination products
- DMEPA will identify the need for and issue inter-center consults to the CDRH Human Factors Team as needed
- DMEPA consults Patient Labeling Team (PLT) in the Office of Medical Policy for the review of layperson directed Instructions for Use (IFU) in the IND phase for products

Use Related Risk Analysis*

- The URRA is a risk management tool that supports the entire HF engineering process and should be utilized as part of an overall risk management framework.
- The URRA informs the HF validation study design, testing and evaluation of a medical product. A use-related risk analysis is important to help identify use-related hazards associated with the combination product, as well as to characterize risks so they can be mitigated or eliminated through improved product user interface design.

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

Human Factors Validation Study Protocol*

- Based on the findings of your URRA, HF data may be needed
- The URRA can inform the design of your HF Validation Study Protocol
- The submission of a HF Validation Study Protocol for Agency review is not required, but encouraged to ensure that your methodology is appropriate to achieve the study's objective

*Draft guidance ***Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications***

Human Factors 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 have been eliminated or that the mitigation for residual risks is acceptable
- The study participants are representative of the intended users and the study conditions are representative of expected use conditions.

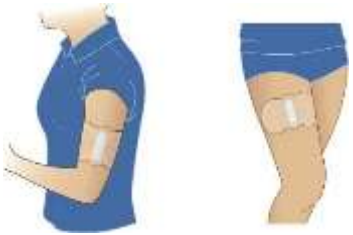
*Draft guidance ***Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development***

Combination Products

- Formal Definition in 21 CFR 3.2:
  - Therapeutic and diagnostic products
  - Combine >1: drugs, devices, biological products
- Combination products can be:
  - Physically or chemically combined (21 CFR 3.2(e)(1))
  - Co-packaged in a kit (21 CFR 3.2(e)(2))
  - Separate, cross-labeled products (21 CFR 3.2(e)(3) or (4))

Combination Product Examples

- Pre-filled IV infusion bags
- Prefilled Syringes
- Pen Injectors, Autoinjectors
- Pharmaceutical Aerosol Delivery Devices/Inhalation Products
- Transdermal Delivery Systems/Patches
- Drug Infusion Devices
- Kits containing drug and administration devices



Human Factors Considerations?

- HF data may be useful to support medical product development, even when the product is not a combination products
  - Novel packaging
  - New user group
  - Complex instructions

Regulatory Authority

Device:
21 CFR 820.30
Requirement of device

effective use

Drug:

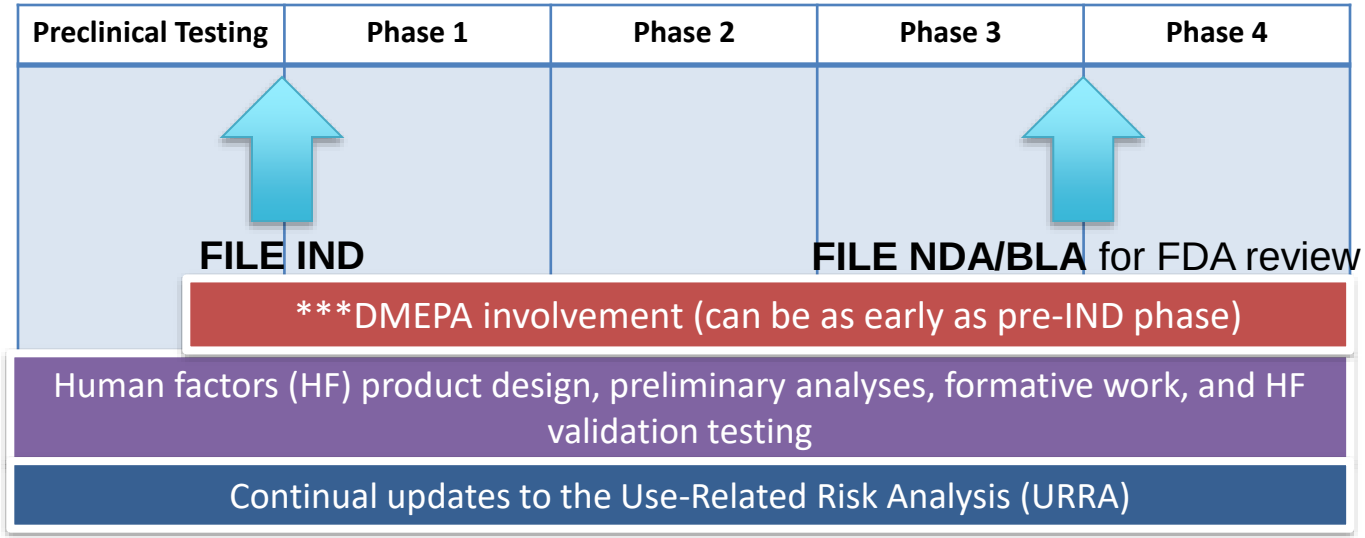
- Kefauver-Harris Amendment to the 1938 Food, Drug and Cosmetic Act

HF studies may be needed to demonstrate elimination/minimization of use-related hazards and medication errors

improved product design including packaging, nomenclature, and labeling

- PDUFA IV development goal: ensure drug safety by prospectively designing a drug that minimizes the risk for errors made by intended end users.

Drug Development Process & Human Factors Considerations for Commercial (to-be-marketed) Product



Your User Interface (UI)* is Not Just the Device

User interface: includes all points of interaction between the product and the user(s) including elements such as displays, controls, packaging, product labels, instructions for use, etc.

*Draft Guidance for Industry: Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA

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BsUFA III/PDUFA VII HF Commitments

BsUFA III HF Commitments

(excerpted from commitment letter)

FDA Performance goals for BsUFA III Human Factors Validation Study Protocol commitment will be as follows:

- Beginning in FY 2023 **(October 1, 2022, to September 30, 2023)**, Review and provide sponsor with written comments for 90% of filed human factors validation **protocol** submissions within 60 days of receipt of protocol submission for biologics**.**

BsUFA III/PDUFA VII HF Commitments

(excerpted from commitment letter)

Staged implementation of review performance goals for **URRA** in PDUFA VII and BsUFA III:

- Review and notify sponsor of agreement or non-agreement with comments within 60 days of receipt for **50%** of filed submissions (**FY2024**: **October 1, 2023 to September 30, 2024**)
- Review and notify sponsor of agreement or non-agreement with comments within 60 days of receipt for **70%** of filed submissions **(FY2025)**
- Review and notify sponsor of agreement or non-agreement with comments within 60 days of receipt for **90%** of filed submissions **(FY2026-FY2027)**

BSUFA III/PDUFA VII HF Commitments

(excerpted from commitment letter)

- By the end of **FY 2024** (**October 1, 2023 to September 30, 2024**), FDA will publish a new draft guidance for review staff and industry describing considerations related to drug-device and biologic-device combination products on the topics noted below:
  - Guidance that will convey FDA's current thinking regarding how a URRA along with other information can be used to inform when the results from an HF validation study may need to be submitted to a marketing application. The guidance will provide a comprehensive, systematic and stepwise approach with examples, when applicable, to illustrate how to make this determination.

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Human Factors Submission Tips for Discussion

1. Unsure of what/if/when HF data needs are required?

- Guidance's are available and references are included at the end of this presentation.
- Early interaction with the Agency to ensure you have prepared for and considered if any HF data needs exist for your proposed product.

2. Response to Previous HF Advice: clarifying questions

Information Request (IR) sent by the Agency to clarify:

- Do you need clarity on recommendations previously made?
- Did you implement all of our recommendations?
- Did you disagree with any of our recommendations?

Response to Previous HF Advice - clarifying questions

- Use the cover letter to communicate your intent.
  - E.g., We have aligned with most of the Agency's recommendations, and seek clarification on recommendations **#4** and **#7**. (example)
- Format the submission using the same table presentation the Agency initially sent; add an additional column with your concerns.

3. Revised HF protocol submitted: What is the intent

IR sent by the Agency to clarify:

- Do you want the Agency to provide another review your revised HF Protocol?
- Do you align with all recommendations and are just submitting a revised protocol for the record?

Revised HF protocol submitted: What is the intent

- Cover letter provides quick details
  - We have aligned with the Agency's recommendations and are submitting the Final HF Protocol for the record. (example)
  - We have determined that our user groups are no longer representative. This revised HF protocol provides a new methodology as well as new user groups. (example)
- Still need to provide comprehensive details in the submission

4. Review of revised HF protocol – presentation of information

IR sent by the Agency to clarify:

- What are the revisions to the methodology?
- What are the revisions to the moderator script?
- Are there any changes to the IFU?
- Do any of the changes require updates to the URRA?

Review of revised HF protocol - presentation of information

- Side by side or red-lined version to highlight changes since our last review could be helpful

5. HF Protocol submission-URRA incomplete or missing

The Agency may find a submission incomplete if:

- URRA is missing
- If the URRA is presented in a way where significant “row data ” is missing, (e.g. not inclusive of all CRITICAL tasks)
- We consider these pieces of information included in the columns below when determining completeness of the URRA:

Task Number	Use task description	Description of potential use error	Potential hazard/clinical harm and severity	Critical task (y/n)	Risk mitigation measure for each use error	Evaluation method

HF Protocol submission-URRA incomplete or missing

Refer to the draft guidance*

- Additional definitions of the terms in the headers below can be found within our guidance. * Please note the tabular presentation is recommended formatting for the URRA submission, but not required.

Task Number	Use task description	Description of potential use error	Potential hazard/clinical harm and severity	Critical task (y/n)	Risk mitigation measure for each use error	Evaluation method

*Draft guidance: ***Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications***

6. HF Protocol submission-user interface

If we do not find the following information in your submission, we may be unable to proceed with the review:

- Description of intended product users, uses, use environments, intended dosing and training (if applicable) for commercial product.
- The graphical depiction of the labels and labeling and written description of product user interface.
- No IFU. Without an IFU, we are unable to determine if all tasks have been considered and evaluated for use-related risk with the proposed product. We are also unable to provide feedback on the appropriateness of the use steps and how the information is formatted .

6. HF Protocol submission-user interface

Refer to the draft guidance*

- Additional information of the what we consider a complete submission is included in the draft guidance.

*Draft guidance: ***Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications***

Challenge Question #1

When determining if your proposed may need HF data you should:

A. Include a narrative of your independent determination once you submit your NDA/BLA

B. Reach out to discuss with the Agency as early as possible and before you submit your NDA/BLA

C. Leave the box on the 356h form unchecked and someone will reach out to you to follow up

D. The FDA does not allow the approval of combination products

Challenge Question #2

Which of the following statements is TRUE?

A. Only combination products require the submission of human factors validation data to support safe use.

B. If you are approved for accelerated approval, your proposed product is exempt from the submission of human factors data

C. It is safe to say that a product proposed in a vial presentation for self-administration will never require human factors data

D. A use-related risk analysis is- important to help identify use-related hazards associated with the combination product, as well as to characterize risks so they can be mitigated or eliminated through improved product interface design

Summary

- With the implementation of PDUFA VII and BsUFA III, the number of HF protocol submissions to the Agency may increase.
- To ensure timely and efficient review, it is imperative that each HF submission is a complete submission
- We recommend you come to us early to seek advice on your HF development plan and to determine if we see any indication to encourage you submit your HF validation study protocol for Agency review.

Closing Thought

Your call to action:

Consider the information presented today in your future submissions to help ensure a complete and timely review

Resources

- Draft guidance: *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-factors-studies-and-related-clinical-study-considerations-combination-product-design-and
- Draft guidance: *Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications:* https://www.fda.gov/media/122971/download

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Questions?