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

Guidance for Industry and FDA Staff

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Quynh Nhu Nguyen, 301-796- 6273, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2018
Procedural

Contains Nonbinding Recommendations

Draft — Not for Implementation

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Additional copies are available from:
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http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications Draft Guidance for Industry and FDA Staff[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

This document provides guidance to industry and FDA staff on the contents of and submission procedures for ***threshold analyses***[2] and human factors (HF) submissions[3] that will support efficient Agency review, and presents timelines for FDA's review of such submissions.[4]

This guidance applies to the following types of products[5]:

- Human prescription drug products, including biologics, that are the subject of an investigational new drug application (IND)[6], a new drug application (NDA), a biologics license application (BLA), or an abbreviated new drug application (ANDA),[7] and supplements to these applications

- Human nonprescription drug products that are the subject of an IND, NDA, or ANDA

[1] This guidance has been prepared by the Office of Surveillance and Epidemiology in the Center for Drug Evaluation and Research (CDER), in cooperation with the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health, and the Office of Combination Products (OCP) at the Food and Drug Administration.

[2] All terms presented in ***bold italic*** at first use in this guidance are defined in the Glossary.

[3] See section III of this guidance for the types of submissions.

[4] This document is one of several documents FDA is issuing to fulfill the performance goals under the sixth authorization of the Prescription Drug User Fee Act (PDUFA VI). This document also provides information on what to include in submissions for products under other user fee programs.

[5] This includes combination products. See definition of combination product in 21 CFR 3.2. For the purposes of this guidance, we are referring to combination products assigned to CDER or CBER as the lead center.

[6] Sponsors can engage FDA on human factors issues as early as the pre-IND phase.

[7] The recommendations in this guidance apply to ANDA submissions covering drug-device combination products.

All such products in this guidance are jointly referred to as *products*,[8] and persons responsible for making submissions are referred to as *sponsors*.

This guidance does not describe when threshold analyses or HF submissions are warranted for any particular application pathway, the processes or procedures associated with their review, or the methods used by the Agency for evaluation. Furthermore, this guidance does not describe the methods used to design, conduct, or analyze HF studies. In addition to the information described in this guidance, FDA recommends that sponsors refer to other relevant guidance documents related to product design and human factors (see section VIII).

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency'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 Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The Federal Food, Drug, and Cosmetic Act (FD&C Act) requires that drug products submitted for approval under section 505(b) be proven safe and demonstrate substantial evidence of effectiveness for the product's intended use (21 U.S.C. 355(b)). Under section 351 of the Public Health Service Act, FDA licenses a biological product based on a demonstration that it is safe, pure, potent, and it is manufactured in a facility designed to ensure that the product continues to be safe, pure, and potent.

As part of evaluating drug and biologic products for safety and effectiveness, FDA will evaluate HF data submitted by sponsors in support of the product ***user interface*** when submission of such data is warranted. For products that sponsors intend to submit as an ANDA, the sponsor can rely on the Agency's previous finding that its listed drug is safe and effective so long as the sponsor can demonstrate certain findings.[9] Certain products, including drug-device combination products, may warrant threshold analyses and additional data, such as data from comparative HF studies.[10]

[8] For purposes of this guidance, unless otherwise specified, references to "products" include drugs submitted for approval or approved under sections 505(b) or 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(b) or 355(j)) and biological products licensed under section 351 of the PHS Act.

[9] See Section 505(j)(2)(A), 505(j)(4) of the FD&C Act (21 U.S.C. 355(j)(2)(a), 355(j)(4)); 21 CFR 314.127.

[10] See draft guidance for industry and FDA staff *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (Comparative Analyses Draft Guidance), available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536959.pdf. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

III. SUBMISSION TYPES, COVER LETTER, AND FDA FORMS

A. Types of Submissions

Listed below are the different threshold analysis and human factors submission types:

1) ***Use-Related Risk Analysis***

2) ***HF Validation Study Protocol***

3) ***HF Validation Study Results Report***

4) ***Threshold Analyses***

5) ***Comparative Use HF Study Protocol***

6) ***Comparative Use HF Study Results Report***

See section IV for information regarding the content of each submission type listed in this section:

B. Cover Letter

Each submission should include a cover letter that includes the statement "**REQUEST FOR [*Type of Submission*] REVIEW**" in bolded capital letters.

For submission amendments, the cover letter should include the statement "**AMENDMENT TO REQUEST FOR [*Type of Submission*] REVIEW**" in bolded capital letters.[11]

See Appendix A for examples.

C. Form FDA 1571 or Form FDA 356h

All electronic submissions should include only fillable forms and electronic signatures to enable automated processing. A submission that is the subject of an active IND should include Form FDA 1571, "Investigational New Drug Application (IND)." A submission that is the subject of a marketing application should include Form FDA 356h, "Application to Market a New or Abbreviated New Drug or Biologic for Human Use." Refer to the FDA Forms website for the latest versions of these forms and their corresponding instruction files.[12]

[11] See section VI for additional considerations for amendments.

[12] See the FDA Forms website for latest versions of forms and instruction files at: http://www.fda.gov/aboutfda/reportsmanualsforms/forms/default.htm.

IV. CONTENTS OF THRESHOLD ANALYSES AND HUMAN FACTORS SUBMISSIONS

This section describes the information that a sponsor should include for each respective submission type.

A. Use-Related Risk Analysis[13]

A comprehensive use-related risk analysis may be a separate submission or may be included as part of another submission (e.g. with the HF validation study protocol (see section IV.B) or Human Factors Engineering (HFE) Report (see section IV.C).[14] The risk analysis submission should include:

- A comprehensive and systematic evaluation of all the steps involved in using the proposed product (e.g., based on a ***task analysis***)
- The errors that intended product ***users*** might commit or the tasks they might fail to perform, taking into consideration known problems with similar products
- The potential negative clinical consequences of ***use errors*** and task failures including the severity of the resulting harm
- User task description and categorization (e.g., critical)
- The mitigation strategies employed to reduce identified risks or eliminate hazards
- The proposed methods used to validate these mitigation strategies
- Description of intended product users, uses, ***use environments***, and training (if applicable)
- Graphical depiction and written description of product user interface (see Appendix C for example)
- Summary of known use problems with previous or similar products[15]

[13] ANSI/AAMI/ISO 14971, *Medical Devices – Application of risk management to medical devices*, defines risk as the combination of the probability of occurrence of harm and the severity of the potential harm. However, because probability is very difficult to determine for use errors, and in fact many use errors cannot be anticipated until product use is simulated and observed, the severity of the potential harm may be more meaningful for determining the need to eliminate (design out) or reduce resulting harm. Therefore, it may be appropriate when conducting the use-related risk analysis to focus on the resulting harm, and including estimated occurrence rates may not be needed.

[14] See guidance *Applying Human Factors and Usability Engineering to Medical Devices* available at https://www.fda.gov/downloads/medicaldevices/.../ucm259760.pdf

[15] In certain circumstances, there may be post-marketing experience that is relevant to the product under consideration. Such information might include known use problems with previous models of the subject product or known use problems with similar products.

- Summary of preliminary analyses and evaluations, including ***formative evaluation***

See Appendix B for an example of how to present some of the key information for a use-related risk analysis.

A sponsor can employ the use-related risk analysis to identify the need for risk mitigation strategies and to design an HF validation study that adequately evaluates the risk mitigation strategies. In circumstances where, based on the use-related risk analysis and other information, a sponsor determines that an HF validation study is not needed, the sponsor may submit the use-related risk analysis and other information, together with the justification for not conducting a HF validation study, for review under the IND.

B. Human Factors Validation Study Protocol

Sponsors should include the following elements in the submission:

1. Background

    - Description of intended product users, uses, use environments, and training (if applicable)

    - Graphical depiction and written description of product user interface (see Appendix C for example), including the intend-to-market ***labels*** and ***labeling*** that will be evaluated in the HF validation study

        - For Instructions for Use (IFUs), in addition to an intended commercial printed layout version, sponsors should provide a Word version to facilitate the exchange of labeling comments and revisions between the sponsor and FDA.[16]

    - Summary of known use problems with previous or similar products[17]

    - Summary of preliminary analyses and evaluations, including formative evaluations; a discussion of key findings; and any changes made to the user interface (e.g., device constituent part design change, labeling changes), as well as a discussion of how the sponsor used the formative evaluation results and findings to update the product user interface and use-related risk analysis

[16] Submitting the IFU document in a Word version is consistent with recommendations to submit labeling content to FDA as part of a marketing application; see draft guidance *SPL Standard for Content of Labeling Technical Qs & As*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[17] In certain circumstances, there may be post-marketing experience that is relevant to the product under consideration. Such information might include known use problems with previous models of the subject product or known use problems with similar products.

2. Analysis of ***hazards*** and risks associated with use of the product in a use-related risk analysis

3. ***HF validation testing*** details

    a. Study objective(s)

    b. Type of testing (***simulated-use*** vs. actual use)[18]

    c. Test environment and conditions[19]

    d. Training provided to participants and rationale for how it corresponds to real-world training and ***training decay*** (if applicable)

    e. Distinct user groups by number and type of test participants[20]

    f. User task description and categorization (e.g., critical)[21] and a description of use scenarios that include critical tasks

    g. Definition of successful performance or failure of each test task

    h. Description of data (e.g., data collected from observational tasks, knowledge tasks, and subjective interview) to be collected and methods for documenting

    i. Methods for root cause analysis of all use errors, difficulties, and ***close calls***[22]

    j. Moderator script

[18] See draft guidance for industry and FDA staff *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development* (Combination Products Human Factors Draft Guidance), available at https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf, for further discussion of simulated vs. actual use studies. When final, this guidance will represent the FDA's current thinking on this topic.

[19] A rationale for how the testing environment and conditions of testing is representative of real-world use is helpful. In identifying conditions of testing, sponsors should consider aspects of use that can be reasonably anticipated, such as use with gloves or wet fingers, in dim lighting, or in noisy situations.

[20] When describing study participants and how they represent distinct user populations (groups), it is helpful to describe the characteristics that distinguish the groups and that can affect user interaction with the product (e.g., limited hand dexterity, cognitive deficit).

[21] The selection of user tasks can be derived from the comprehensive use-related risk analysis. Tasks that could lead to harm (e.g., underdose or overdose), including those requiring the user to respond to alerts or alarms, should be categorized as critical and prioritized for testing. A task requiring comprehension of warnings, caution statements, or contraindications in the product labels or labeling would generally be considered a critical knowledge task. See Combination Products Human Factors Draft Guidance), available at https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf, for definition of critical tasks.

[22] While close calls and difficulties may not manifest into use errors/task failures, they are good sources of data in terms of providing potential user interface inadequacies that should be further evaluated.

4. Product samples (5 samples of product that will be tested in the HF validation)[23]

C. Human Factors Validation Study Report[24]

Sponsors should include the following elements in their submission:

1. Summary of findings and conclusions

    a. Conclusions based on HFE process[25]

    b. Brief summary of validation study results

    c. Discussion of whether additional risk mitigation measures are necessary

        i. If additional mitigation measures are needed, the study report should include a description of the additional mitigation measures and justify whether additional validation testing is not warranted. However, if additional validation testing is needed, the results should be submitted within the report.

    d. Discussion of ***residual use-related risks*** versus benefits of the product

2. Background[26]

    a. Brief summary of ***Human Factors Engineering*** processes applied throughout the development of the product

    b. Descriptions of intended product users, uses, use environments, and training (if applicable)

    c. Graphical depiction and written description of user interface (see Appendix C), including the intend-to-market labels and labeling that were evaluated in the HF validation study

[23] FDA recognizes that in some circumstances, the ability to provide the requested quantity of samples may not be feasible. In this instance, we recommend you contact FDA for further guidance.

[24] The contents of the HF validation study report are intended to be equivalent to the contents outlined in Appendix A of the guidance *Applying Human Factors and Usability Engineering to Medical Devices*.

[25] If the HFE process identifies no use errors or problems that could result in harm, the sponsor should discuss how the validation study results supports a conclusion of safe and effective use by the end user. Otherwise, the sponsor should include a discussion of why the existing mitigations are effective and why the Agency should find the residual risks acceptable in the report. The discussion should incorporate findings from the entire HFE process.

[26] If previously submitted, cross-reference the prior submission and include the eCTD sequence number and date of submission. Sponsors should not resubmit the electronic files when referencing that document.

d. Summary of known use problems with previous products or similar products

e. Summary of preliminary analyses and evaluations, including formative evaluations

i. The summary should include a discussion of key findings and any changes made to the product design and its labeling based on key findings, and should explain how the sponsor used the formative results and findings to update the product user interface and risk analysis.

f. Reference to previous HF validation study protocol submission, description of changes made to the protocol after prior feedback from the FDA, and description of any protocol deviations that occurred during the study

3. Analysis of hazards and risks associated with use of the product in a use-related risk analysis[27]

4. HF validation testing details

a. Study objective(s)

b. Rationale for test type selected (simulated-use or actual use)[28]

c. Test environment and conditions of use

d. Training provided to test participants and how it will correspond to real-world training levels and training decay (if applicable)

e. Distinct user groups broken out by number and type of test participants

f. ***User tasks*** description and categorization and a description of use scenarios that include critical tasks

g. Definition of successful performance or failure of each test task

h. Test results and analysis (see example in Appendix D)

i. Observations of task performance, including occurrences and description of use errors, close calls, and use difficulties

[27] If previously submitted, cross-reference the prior submission and include the eCTD sequence number and date of submission. Sponsors should not resubmit the electronic files when referencing that document.

[28] See Combination Products Human Factors Draft Guidance for further discussion of simulated vs. actual use studies. When final, this guidance will represent the FDA's current thinking on this topic

ii. Documentation of subjective data from study participants regarding product use, use errors, close calls and use difficulties.
iii. Root cause analysis of all use errors, difficulties, and close calls and discussion of risk mitigation strategies

5. Product samples (5 samples of intend-to-market product) [29]

D. Threshold Analyses

Threshold analyses generally are utilized in comparing two drug products. For these analyses, sponsors should include the following elements in their submission:

1. Labeling comparison (a side-by-side, line-by-line comparison between the proposed product and the product it references that includes the full prescribing information, instructions for use, container labels and carton labeling, and descriptions of the products)

2. Comparative task analysis[30] (a comparative task analysis of the proposed product and the product it references)

3. Physical comparison of the device constituent part(s) (e.g., examine, through a visual or tactile examination, the physical features of the product that it plans to reference and compare them to those of the proposed product)

4. Sponsor's determination of whether design differences exist and, if so, whether they are characterized as minor design differences or other design differences,[31] and the rationale for each characterization

[29] FDA recognizes that in some circumstances, the ability to provide the requested quantity of samples may not be feasible. In this instance, we recommend you contact FDA for further guidance.

[30] To conduct a comparative task analysis, sponsors should systematically dissect the use process for each product (i.e., for both the proposed product and the product it references) and analyze and compare the sequential and simultaneous manual and cognitive activities for end-users interacting with each product. FDA recommends that sponsors analyze the differences with the goal of characterizing the potential for use error. See the Association for the Advancement of Medical Instrumentation/American National Standards Institute HE75: 2009-Human factors engineering—Design of medical devices, available at: http://my.aami.org/aamiresources/previewfiles/HE75_1311_preview.pdf. Presenting this information in a side-by-side comparison table can help to facilitate FDA evaluation of this information.

[31] For further discussion on identifying design differences and characterizing design difference(s), see Comparative Analyses Draft Guidance, available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536959.pdf and draft guidance for industry *Considerations in Demonstrating Interchangeability With a Reference Product, available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf*. When final, these guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

5. Product samples (5 samples each of the proposed product and the product it references)[32]

E. Comparative Use Human Factors Study Protocol[33]

Sponsors should include the following elements in their submission:

1. Background, including description of the intended product users, uses, and use environments

2. Threshold analyses (see section IV.D, above)[34]

3. Comparative use HF testing details

    a. Study objective(s)

    b. Type of testing (simulated-use vs. actual use)[35]

    c. Statistical analysis plan (SAP) and sample size considerations (including proposed analyses and all assumptions, as well as literature references or other justification supporting the methods or assumptions)

    d. Test environment and conditions of testing

    e. Distinct user groups broken out by number and type of test participants

    f. User task description and categorization (e.g., critical)[36] and a description of use scenarios that include critical tasks

    g. Definition of successful performance or failure of each test task

    h. Description of data (e.g., data collected from observational tasks, knowledge tasks, and subjective interview) to be collected and methods for documenting

[32] FDA recognizes that in some circumstances, the ability to provide the requested quantity of samples may not be feasible. In this instance, we recommend you contact FDA for further guidance.

[33] Potential applicants intending to submit a drug-device combination product under an ANDA are strongly encouraged to discuss the results of the threshold analyses with the Agency via the controlled correspondence or pre-ANDA submission pathways, or both, prior to conducting comparative use human factors studies.

[34] If previously submitted, cross-reference the prior submission and include the eCTD sequence number and date of submission. Sponsors should not resubmit the electronic files when referencing that document.

[35] See Combination Products Human Factors Draft Guidance for further discussion of simulated vs. actual use studies.

[36] In some instances, it may be appropriate to focus the selection of user tasks on the critical tasks related to the external critical design attributes found to be different between the proposed product and the product it references.

i. Methods for evaluating error rates

j. Moderator script

4. Product samples (5 samples each of the proposed product and the product it references that will be tested in the comparative use HF study) [37]

F. Comparative Use Human Factors Study Results Report

Sponsors should include the following elements in the submission:

1. Summary of study findings and conclusions

   - Conclusions[38]

   - Brief summary of study results

2. Background[39]

   a. Descriptions of intended product users, uses, and use environments

   b. Reference to previous protocol submission, description of changes made to the protocol after prior feedback from the FDA, and description of any protocol deviations that occurred during the study

3. Threshold analyses (see section IV.D, above)[40]

4. Comparative use HF testing details

   a. Study objective(s)

   b. Rationale for test type selected (simulated-use or actual use) [41]

[37] FDA recognizes that in some circumstances, the ability to provide the requested quantity of samples may not be feasible. In this instance, we recommend you contact FDA for further guidance.

[38] A comparative use human factors study should be designed to provide sufficient data to confirm that the use error rate for the critical task(s), as impacted by the differing external critical design attribute of the device constituent part(s) for the proposed generic combination product, is not worse than the corresponding use error rate for the RLD when used by patients and caregivers in representative use scenarios and use environments consistent with the labeled conditions of use. See Comparative Analyses Draft Guidance for further discussion.

[39] If previously submitted, cross-reference the prior submission and include the eCTD sequence number and date of submission. Sponsors should not resubmit the electronic files when referencing that document.

[40] If previously submitted, cross-reference the prior submission and include the eCTD sequence number and date of submission. Sponsors should not resubmit the electronic files when referencing that document.

[41] See Combination Products Human Factors Draft Guidance for further discussion of simulated vs. actual use studies.

c. SAP and sample size considerations (including analyses and all assumptions, as well as literature references or other justifications supporting the methods or assumptions)

d. Test environment and conditions of use

e. Distinct user groups broken out by number and type of test participants

f. Critical tasks and use scenarios included in testing

g. Definition of successful performance or failure of each test task

h. Test results and analysis

i. Use error rates and analysis

ii. Observations of task performance, including occurrences of use errors

V. WHERE TO SEND A THRESHOLD ANALYSIS OR HUMAN FACTORS SUBMISSION

Generally, FDA expects that sponsors will submit threshold analyses or HF submissions consistent with the respective regulatory pathway. Sponsors should submit an HF validation study protocol and questions regarding the protocol to the IND. For proposed generic products, sponsors should submit threshold analyses, device assessments, and questions via the controlled correspondence or pre-ANDA submission pathways, or both, as appropriate. Comparative use HF study protocols should be submitted within a specific pre-ANDA meeting request. It is recommended that all sponsors plan their development timelines to allow for Agency feedback on protocols prior to initiation and conduct of the appropriate HF study. In addition, sponsors should submit HF validation study results reports or comparative use HF study results reports in their application for FDA review (i.e., NDA, BLA, or ANDA).

Submissions to a Commercial IND, NDA, BLA, or ANDA must be made in Electronic Common Technical Document (eCTD) format.[42] Submissions to a Research IND[43] may be in paper or electronic format. For paper submissions, sponsors should submit 3 copies to the appropriate address below.

[42] See guidance for industry *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (Using eCTD Specifications Guidance); see also section 745A(a) of the FD&C Act (21 U.S.C. 379k-1(a)).

[43] See FDA's web page on Investigational New Drug (IND) Application at https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm.

A. Drug Products, Including Biologics, and Combination Products, That Are the Subject of an IND Paper Submission

1. *Human Factors Submissions for Prescription or Nonprescription Drugs, Including Biologics, That Are the Subject of an IND Reviewed by CDER*

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

2. *Human Factors Submissions for Prescription or Nonprescription Biologics That Are the Subject of an IND Reviewed by CBER*

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
Bldg. 71, Rm. G112
Silver Spring, MD 20993-0002

B. Drug-Device Combination Products Under Development for Submission Under ANDA

1. *Controlled Correspondence*

Sponsors seeking FDA's feedback on a specific element in the development of a drug-device combination product (e.g., identification and assessment of identified differences between the user interface of a proposed generic combination product and its reference listed drug) should submit the correspondence through the process outlined in FDA's draft guidance *Controlled Correspondence Related to Generic Drug Development*.[44] This will facilitate prompt consideration of and response to the controlled correspondence by the appropriate discipline.

2. *Pre-ANDA Meeting*

A request for a product development or pre-submission meeting for complex products that may be submitted in an ANDA should be sent through the process outlined in FDA's draft guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (Generic Drug User Fee Act). The meeting request should clearly identify in the subject line that the prospective applicant is requesting a product development or pre-submission

[44] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

meeting and should include adequate information for FDA to assess the potential utility of the meeting and identify the appropriate staff that should attend the meeting.

C. Electronic Submissions

The sponsor should place the request for HF submission review in Module 1.2 and associated documents (e.g. use-related risk analysis, protocols, reports) in Module 5, section 5.3.5.4 – Other Study Reports and Related Information in eCTD.

The eCTD leaf title of the document should be clear, concise, and indicative of the content. Examples include:

- HF - REQUEST FOR HUMAN FACTORS VALIDATION STUDY PROTOCOL REVIEW
- HF - AMENDMENT TO REQUEST FOR HUMAN FACTORS VALIDATION STUDY PROTOCOL REVIEW
- HF - REQUEST FOR HUMAN FACTORS VALIDATION STUDY REPORT REVIEW
- HF - AMENDMENT TO REQUEST FOR HUMAN FACTORS VALIDATION STUDY REPORT REVIEW
- HF-REQUEST FOR HUMAN FACTORS VALIDATION OTHER REVIEW[45]
- HF-AMENDMENT TO REQUEST FOR HUMAN FACTORS VALIDATION OTHER REVIEW

The sponsor should also provide the eCTD location of the contents of the HF submission on the cover letter and, if possible, include cross-document links or external bookmarks to the information. This approach will help ensure that the information can be accessed quickly and easily. For further information on providing leaf titles and study results reports (including file-tags) in eCTD, see the eCTD Technical Conformance Guide.[46]

VI. REVIEW TIMELINE

[45] For the purposes of the eCTD, there are three options: protocols, reports, or other. "Other" includes use-related risk analyses and threshold analyses.

[46] The eCTD Technical Conformance Guide is available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm.

The Agency intends to review and comment on HF validation study protocol submissions in accordance with PDUFA VI performance goals.[47] The review clock for the performance review goals begins when the Agency receives a ***complete submission***. FDA will:

- By fiscal year (FY) 2019, review 50% of HF protocol submissions and provide the sponsor with written comments within 60 days
- By FY 2020, review 70% of HF protocol submissions and provide the sponsor with written comments within 60 days
- By FY 2021, review 90% of HF protocol submissions and provide the sponsor with written comments within 60 days

If, after submitting an HF validation study protocol, a sponsor submits additional questions, unsolicited revisions to the protocol, or a lengthy or complex response to an FDA question, or amends original submission materials with new information for any reason, FDA ordinarily will not respond to the original questions and will consider the original protocol submission withdrawn. FDA will consider submission of a revised protocol, or revised or additional supporting materials, to be a new submission with a new 60-day timeline for response.

FDA will review all threshold analyses or comparative use HF submissions consistent with good review management principles and practices, as applicable, and in a timeframe to support any applicable performance goals under FDA's various user fee programs, taking into consideration the specific circumstances (e.g. breakthrough designation) surrounding the individual application.

VII. HOW TO OBTAIN ADDITIONAL INFORMATION

FDA encourages industry to meet with the Agency when appropriate[48] to obtain Agency advice during product development. Meetings should not be used to obtain Agency review of HF validation study protocols or reports.

Prior to submitting an ANDA for a generic combination product, sponsors are encouraged to submit a controlled correspondence[49] or pre-ANDA meeting package, or both,[50] when appropriate.

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[47] *PDUFA VI reauthorization performance goals and procedures for fiscal years 2018 through 2022*, Section I.1.5.e, available at: http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM511438.pdf.

[48] Please refer to Guidance for Industry *Formal Meetings between FDA and Sponsors or Applicants, available at:* https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.pdf.

[49] Draft guidance for industry, *Controlled Correspondence Related to Generic Drug Development, available at:* https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm583436.pdf. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[50] Please refer to draft guidance for industry, *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*, available at

VIII. REFERENCES

Applicable guidance documents relating to HF, product design, requesting meetings with the Agency, and providing electronic submissions include those listed below:

A. Guidance documents related to HF

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

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

- Draft guidance for industry *Considerations in Demonstrating Interchangeability With a Reference Product*

- Guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices*

B. Guidance documents related to product design

- Guidance for industry *Safety Considerations for Product Design to Minimize Medication Errors*

- Draft guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*

C. Guidance on requesting meetings with Agency

- Draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*

- Draft guidance for industry, *Controlled Correspondence Related to Generic Drug Development*

- Draft guidance for industry, *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm578366.pdf. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

- Guidance for industry and review staff *Best Practices for Communication Between IND Sponsors and FDA During Drug Development*

D. Guidance on providing electronic submissions

- Guidance for industry *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*

GLOSSARY

Applicant or sponsor: The entity that submits proposed Threshold Analyses or HF submissions for the following types of products:

- Prescription drug products (including biologics) that are the subject of an NDA (21 CFR 314.3(b)), a BLA (21 CFR 601.2), or an ANDA (21 CFR 314.92), or that are currently the subject of an IND (21 CFR 312.3(b)) in anticipation of the submission of a marketing application

- Nonprescription drug products that are the subject of an IND, NDA, or ANDA

Close calls: Instances in which a user almost makes a use error that could result in harm, but the user takes an action to "recover" and prevent the use error from occurring.

Comparative Use Human Factors Study Protocol: A study protocol for a proposed combination product that describes the design and methodology for a comparative use human factors study.

Comparative Use Human Factors Study Results Report: A study report that provides the results of a comparative use human factors study.

Complete submission: The information FDA identifies for a sponsor to include to ensure that the Agency can conduct a complete review of a proposed Human Factors Validation Study Protocol.

Critical task: A user task which, if performed incorrectly or not performed at all, may cause harm to the patient or user, where "harm" includes compromised medical care.

Formative evaluation: The process of assessing, at one or more stages during the product development process, a user interface or user interactions with the user interface in order to identify the interface's strengths and weaknesses and to identify potential use errors that would or could result in harm to the patient or user.

Hazard: A potential source of harm.

Human Factors Engineering: The application of knowledge about human behavior, abilities, limitations, and other characteristics of medical device users when designing medical devices, including mechanical and software-driven user interfaces, systems, tasks, user documentation, and user training, to demonstrate and enhance safe and effective use. HF engineering and usability engineering can be considered synonymous.

Human Factors Validation Study Protocol: A study protocol that describes the design and methodology for a human factors validation study.

Human Factors Validation Study Results Report: A study report that provides the results of a human factors validation study.

Human factors validation testing: Testing conducted at the end of the product development process to assess user interactions with a product user interface and to identify use errors that may result in serious harm to the patient or user. Human factors validation testing is also used to assess the effectiveness of risk management measures. Human factors validation testing represents one portion of design validation.

Label: As defined in section 201(k) of the FD&C Act (21 U.S.C. 321(k)), the term *label* means "a display of written, printed, or graphic matter upon the immediate container of any article."

Labeling: As defined in section 201(m) of the FD&C Act (21 U.S.C. 321(m)), the term *labeling* means "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." Labeling includes outside containers or wrappers and package liners.

Medication error: The National Coordinating Council for Medication Error Reporting and Prevention describes *medication error* as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.[51]

Residual use-related risks: The risks that remain after risk control measures have been taken.

Simulated-use testing: Testing of a product under conditions of use that mimic real-world use conditions without administering the actual therapy to patients.

Task: An action or set of actions performed by a user to achieve a specific goal.

Task Analyses: A systematic breakdown of device use process into discrete sequences of tasks.[52]

Threshold analyses: Conducted to identify differences (if any) that may exist between the proposed combination product's user interface and the product it references. Consist of labeling comparison, comparative task analysis, and physical comparison of the device constituent part(s).[53]

[51] National Coordinating Council for Medication Error Reporting and Prevention web page, available at: http://www.nccmerp.org/aboutMedErrors.html.

[52] See an example of a task analysis in Guidance for Industry and FDA Staff titled "Applying Human Factors and Usability Engineering to Medical Devices," available at https://www.fda.gov/downloads/MedicalDevices/.../UCM259760.pdf.

[53] See Comparative Analyses Draft Guidance.

Training decay: The time elapsed between receiving training and first product use**.**

Use environment: The environment(s) in which the product will be used. This may include a variety of settings, such as clinical settings or home settings.

Use error: A user action, or lack of action, that was different from that expected by the manufacturer and that caused an outcome that (1) was different from the result expected by the user, (2) was not caused solely by product failure, and (3) did or could result in harm.

Use-related risk analysis: An analytical method to identify use errors associated with each use step, and then the hazards/risks and clinical significance of those hazards/risks. The use-related risk analysis includes a comprehensive and systematic evaluation of all the steps involved in using the product (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform (considering known problems for similar products), the potential negative clinical consequences of use errors and task failures, the mitigation strategies, and methods for validating the risk mitigation strategies.

User: A person who interacts with (i.e., operates or handles) the product.

User interface: All components of the product with which the user interacts, including the device constituent part(s) of the product and any associated controls and displays, as well as product labels, labeling, and packaging.

APPENDIX A

EXAMPLE OF STATEMENTS TO INCLUDE IN THE COVER LETTER

1) For use-related risk analysis reviews, include the statement "**REQUEST FOR USE-RELATED RISK ANALYSIS REVIEW**" in bold capital letters.

2) For amendments to use-related risk analysis reviews, include the statement "**AMENDMENT TO REQUEST FOR USE-RELATED RISK ANALYSIS REVIEW**" in bold capital letters.

3) For HF protocol reviews, include the statement "**REQUEST FOR HUMAN FACTORS VALIDATION STUDY PROTOCOL REVIEW**" in bold capital letters.

4) For amendments to HF protocols, include the statement "**AMENDMENT TO REQUEST FOR HUMAN FACTORS VALIDATION STUDY PROTOCOL REVIEW**" in bold capital letters.

5) For HF study results reports, include the statement "**REQUEST FOR HUMAN FACTORS VALIDATION STUDY REPORT REVIEW**" in bold capital letters.

6) For amendments to HF study results reports, include the statement "**AMENDMENT TO REQUEST FOR HUMAN FACTORS VALIDATION STUDY REPORT REVIEW**" in bold capital letters.

7) For comparative use HF threshold analyses reviews, include the statement "**REQUEST FOR THRESHOLD ANALYSES REVIEW**" in bold capital letters.

8) For amendments to comparative use HF threshold analyses reviews, include the statement "**AMENDMENT TO REQUEST FOR THRESHOLD ANALYSES REVIEW**" in bold capital letters.

9) For comparative use HF protocol reviews, include the statement "**REQUEST FOR COMPARATIVE USE HUMAN FACTORS PROTOCOL REVIEW**" in bold capital letters.

10) For amendments to comparative use HF protocol reviews, include the statement "**AMENDMENT TO REQUEST FOR COMPARATIVE USE HUMAN FACTORS PROTOCOL REVIEW**" in bold capital letters.

11) For comparative use HF study results report reviews, include the statement "**REQUEST FOR COMPARATIVE USE HUMAN FACTORS REPORT REVIEW**" in bold capital letters.

12) For amendments to comparative use HF study results report review, include the statement "**AMENDMENT TO REQUEST FOR COMPARATIVE USE HUMAN FACTORS REPORT REVIEW**" in bold capital letters.

APPENDIX B

EXAMPLE OF USE-RELATED RISK ANALYSIS

Task No.	Use task description	Description of potential use errors	Potential hazards/harm and severity[54]	Critical task (Yes/ No)	Risk mitigation measure for each use error	Evaluation method in HF validation study
4	Press green button and hold for 10 seconds	Button is held for less than 10 seconds	Full dose is not injected; leads to patient death	Yes	Redesign product to eliminate the need to hold for 10 seconds	Evaluated in HF validation study in use scenario 1: Administration of Drug, task 4

APPENDIX C

EXAMPLE OF DESCRIPTION OF USER INTERFACE

Interface Item	Written description of the user interface	Graphical depiction of the user interface
Inspection Window	The user inspects the window to ensure that the drug color is clear and drug solution does not have any particulates	

[54] Describe potential hazard/harm and severity for each potential use error.

751 **APPENDIX D**
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753 **HYPOTHETICAL EXAMPLE OF HF VALIDATION DATA**
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755 A hypothetical example of the results of analyzing human factors validation study data are
756 shown in the table below. Analysis of human factors validation study data should focus on any
757 problems found during the testing. The study data should be analyzed to determine which part of the
758 user interface was involved and how the user interaction could have resulted in the use error or
759 problem.
760

Description of Tasks (denote C for critical)	Number of use errors and description of use errors	Number of close calls and use difficulties[55] and description of close calls and use difficulties	Study participant's subjective feedback [56]	Sponsor's Root cause analysis[57]	Sponsor's Discussion of Mitigation strategies[58]
Task 4: Press green button and hold for 10 seconds (C)	1 use error. The user did not press the green button for 10 seconds, he only held it for 5 seconds.	0 close calls or use difficulties	The user heard a second click and stopped pressing the button because he thought the injection was complete based on the click.	Root cause analysis showed that the user interface has audible cues that do not coincide with the labeled hold time and contribute to confusion.	Product was redesigned to align the audible cues to the "hold time" needed to deliver the drug. This change impacts a critical task for drug delivery. Thus, the change was evaluated in another validation study conducted to demonstrate the effectiveness of this change to the user interface.

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[55] While close calls and difficulties may not manifest into actual use errors/failures, they are good source of data in terms of providing potential user interface inadequacies that should be further evaluated.

[56] What the participant(s) say about the use errors/close calls/use difficulties from their perspective.

[57] This should incorporate the sponsor's analysis of the subjective data obtained from study participants clarifying why or how the use errors and failures occurred from the participant's perspective. Some questions to consider: What did study participants say about the errors/failures? Did they say how/why the errors/failures occurred? Did they comment on any aspect of the user interface that may have influenced their behavior/action while they were performing the task? Did they note any suggested user interface improvements?

[58] This should address whether additional product modifications, risk mitigations, or risk mitigation validation should be implemented as necessary.