On February 2, 2024, FDA published the final rule to amend the Quality System (QS) regulation in 21 CFR part 820 (89 FR 7496, effective February 2, 2026). The revised 21 CFR part 820 is now titled the Quality Management System Regulation (QMSR). The QMSR harmonizes quality management system requirements by incorporating by reference the international standard specific for medical device quality management systems set by the International Organization for Standardization (ISO), ISO 13485:2016. The FDA has determined that the requirements in ISO 13485 are, when taken in totality, substantially similar to the requirements of the QS regulation, providing a similar level of assurance in a firm's quality management system and ability to consistently manufacture devices that are safe and effective and otherwise in compliance with the Federal Food, Drug, and Cosmetic Act (FD&C Act).

This guidance document was issued prior to the effective date of the final rule. FDA encourages manufacturers to review the current QMSR to ensure compliance with the relevant regulatory requirements.

The QMSR includes conforming edits to 21 CFR part 4 subpart A, *Current Good Manufacturing Practice Requirements for Combination Products*, to clarify the device quality management system requirements for combination products.

Application of Human Factors Engineering Principles for Combination Products: Questions and Answers

Guidance for Industry and FDA Staff

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Contains Nonbinding Recommendations

Application of Human Factors Engineering Principles for Combination Products: Questions and Answers Guidance for Industry and FDA Staff

This guidance represents 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 office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This document contains questions and answers for industry and FDA staff on the application of human factors engineering (HFE) principles to the development of combination products as defined under 21 CFR part 3.[1] This guidance finalizes the February 2016 draft version entitled *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development.* This guidance provides information in a question and answer format and clarifies how the unique aspects of a combination product influence the considerations within the HFE process.

This guidance should be used in conjunction with the guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices*[2] and with the guidance for industry *Safety Considerations for Product Design to Minimize Medication Errors.*[3] Additionally, this guidance supplements other existing guidance documents developed by the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), the Center for Drug Evaluation and Research (CDER), and the Office of Combination Products (OCP) that describe other aspects of product development.

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.

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[1] For additional information on combination products see https://www.fda.gov/combination-products. Applicants with questions on combination product center assignment should contact the Office of Combination Products (combination@fda.gov).

[2] February 2016. For additional information on human factors evaluation for medical devices, see the draft guidance for industry and FDA staff *Content of Human Factors Information in Medical Device Marketing Submissions* (December 2022). When final, that guidance will represent FDA's current thinking on the topic. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[3] April 2016.

II. SCOPE

This guidance focuses on considerations for the application of HFE principles to combination products comprised of a medical device[4] combined with a drug or a biological product submitted for review in CBER, CDRH, or CDER.[5] This guidance discusses, among other things, the definition of a combination product critical task, considerations for combination products due to the use of drug and device constituent parts[6] together, training as part of the user interface, and human factors (HF) validation data to support the combination product user interface that may be included in a premarket submission.

Consistent with development of medical devices, the successful development of a combination product that includes a device constituent part applies the appropriate HFE principles and processes throughout the entire product development process and product lifecycle changes. Because the application of HFE principles and processes is similar for such combination products and medical devices, this document does not focus on general HFE principles or the general design considerations for formative and validation studies.[7]

This document does not address HF considerations for combination products submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act in an abbreviated new drug application (ANDA)[8] or submitted in a BLA under section 351(k) of the Public Health Service Act for a proposed biosimilar or interchangeable biosimilar biological product.[9] This document

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[4] For purposes of this guidance, the term *medical device* is used interchangeably with the term *device* and has the same meaning as this term which is defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act.

[5] As appropriate for the center, the application types include an investigational device exemption application (IDE), investigational new drug application (IND), biologics license application (BLA) submitted under section 351(a) of the Public Health Service Act, new drug application (NDA), premarket approval application (PMA), De Novo classification request, and premarket notification (510(k)). For information on the application types within a center, contact the respective center product jurisdiction officers at CDERProductJurisdiction@fda.hhs.gov, CDRHProductJurisdiction@fda.hhs.gov, or CBERProductJurisdiction@fda.hhs.gov. For further information on what application type may be appropriate for a combination product, see the guidance for industry and FDA staff *Principles of Premarket Pathways for Combination Products* (January 2022).

[6] For purposes of this guidance, the term *drug* also refers to a biological product and the term *drug constituent part* also refers to a biological product constituent part unless otherwise indicated. See 21 CFR 4.2 for the definition of *constituent part*.

[7] For information on general HFE principles and general design considerations for formative and validation studies, see the guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices.* See also the guidance for industry *Safety Considerations for Product Design to Minimize Medication Errors.*

[8] Although human factors considerations for combination products submitted in an ANDA are beyond the scope of this guidance, certain principles described in this guidance may apply to these products on a case-by-case basis. Applicants preparing to submit a combination product for review in an ANDA are strongly encouraged to contact FDA via controlled correspondence and/or a pre-ANDA meeting request to discuss the applicant's proposed product. For additional information, see the draft guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January 2017). When finalized this guidance will represent FDA's current thinking on this topic.

[9] Applicants preparing to submit a combination product for review in a BLA under section 351(k) are encouraged to interact with FDA. For additional information, see the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products* (August 2023). When finalized this guidance will represent FDA's current thinking on this topic. For related information, see Q-15.

does not address label comprehension studies for non-prescription uses.[10] Further, this document does not address when an HF study may be subject to the requirements under 21 CFR part 50 (human subject protection), part 56 (review and approval by an institutional review board (IRB)), part 312 (investigational new drug applications), or part 812 (investigational device exemptions) or how HF studies are considered in user fee determinations.[11]

III. BACKGROUND

Combination products, as described in 21 CFR part 3, are comprised of two or more different types of products (i.e., a combination of a drug, device, and/or biological product with one another). The regulatory requirements for combination products arise from the statutory and regulatory requirements applicable to drugs, devices, and biological products, which retain their discrete regulatory identities when they are constituent parts of a combination product.[12] At the same time, combination products comprise a distinct category of products that can be subject to specialized regulatory requirements, where appropriate.[13]

Medical devices are subject to design control requirements identified in 21 CFR 820.30 that include design validation and a risk analysis where appropriate.[14] As codified at 21 CFR 4.4(b)(1)(ii), Current Good Manufacturing Practice Requirements for Combination Products, combination products that include a device constituent part are subject to design controls.[15] In the context of a drug-device combination product, as part of the HFE process, design controls should include a use-related risk analysis (URRA) of the combination product as a whole, not just the device constituent part or the drug constituent part for its use in the combination product (Figure 1).

Further, beyond use-related risks associated with the device alone, there can be use-related risks associated with the drug. Also, there may be use-related risks associated with the combination product as a whole that do not exist for the device alone or drug alone. These different use-related risks may influence the user interface design inputs and the HFE assessment.

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[10] If your combination product includes a non-prescription drug, the following guidance on this topic may be helpful: guidance for industry *Label Comprehension Studies for Nonprescription Drug Products* (August 2010).
[11] For information on user fee assessment under the Prescription Drug User Fee Act (PDUFA) for applications containing clinical studies, see the guidance for industry *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees* (December 2004). For related information, see Q-15.
[12] See combination product current good manufacturing practice and post marketing safety reporting rules, 78 FR 4307-23 (2013) (21 CFR part 4, subpart A) and 81 FR 92603-26 (2016) (21 CFR part 4, subpart B).
[13] Ibid.
[14] See 21 CFR 820.30(g).
[15] Also, see guidance for industry and FDA staff *Current Good Manufacturing Practice Requirements for Combination Products* (January 2017).

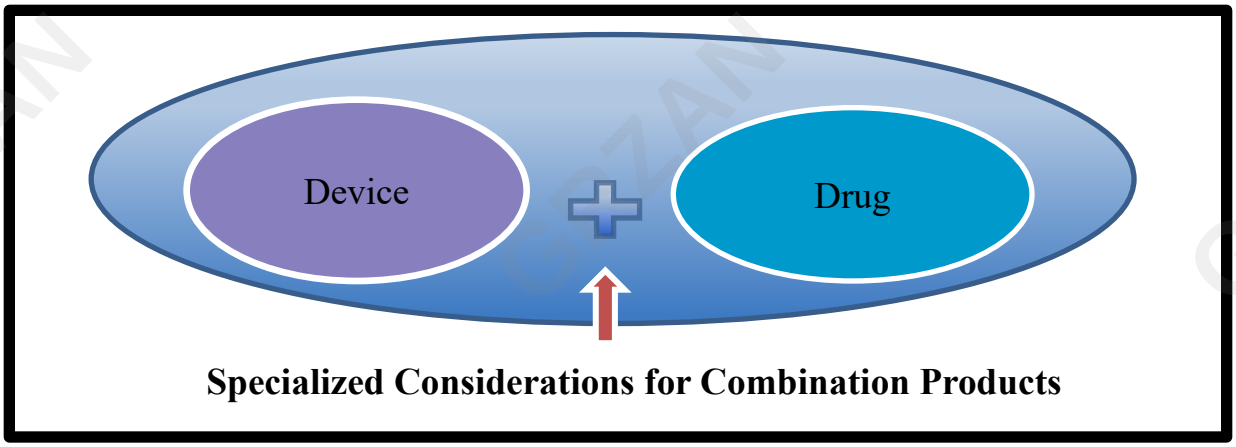


Figure 1: Drug-Device Combination Product Risk Considerations

HFE is the application of knowledge about human behavior, abilities, limitations, and other characteristics of the users to the design of products to help ensure safe and effective use of the product.[16] This includes consideration of the intended user population characteristics, including concomitant diseases and conditions, and limitations that may impact the use of the combination product. For example, for a digital health combination product intended for use in a geriatric patient population, common characteristics or limitations may include decreased vision/hearing, varying literacy levels, and cognitive decline. Furthermore, the design of the combination product should take into account, among other things, the use environment(s), including any limitations (e.g., limited internet /cellular phone service).

A key goal of applying HFE principles during development is to ensure that the user interface supports the safety and effectiveness of the combination product as a whole. The user interface for a combination product includes all points of interaction between the combination product and the user(s), including displays, controls, packaging, product labels, carton labeling, instructions for use, and training, if applicable. Applicants should consider how the design of the user interface could affect the user interactions with the combination product and result in harm, including an interaction that could result in a medication error.[17]

The following questions and answers address certain topics relevant to HFE considerations for combination products, including how the characteristics of drug and device constituent parts, user population(s), and potential for medication errors inform the design of the combination product user interface and impact HFE considerations for combination products.

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[16] See definition in the guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices*, section III.

[17] The guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022), defines a medication error as "any preventable event that may cause or lead to inappropriate medication use or medication-related patient harm while the medication is in the control of the health care professional, patient, or consumer" (see also the National Coordinating Council for Medication Error Reporting and Prevention, https://www.nccmerp.org/about-medication-errors).

IV. QUESTIONS AND ANSWERS

Q-1. What guidance is available for medication error considerations to inform the design of a combination product?

The guidance for industry *Safety Considerations for Product Design to Minimize Medication Errors* provides a set of principles for using a systems approach to minimize medication errors relating to product design, including container closure design, to enhance patient safety. That guidance further explains how HFE principles apply to the design of medical products to minimize medication errors, including those that may lead to patient harm, and provides examples of medical product designs that have resulted in postmarket medication errors.[18]

Q-2. Could a drug's properties affect how a user interacts with a combination product that includes that drug?

Yes, the drug's properties may influence and affect whether a user can successfully complete tasks when using the combination product. For example, the presence of a chemically irritating drug or a viscous drug formulation in combination with an injector-device may increase the risk for local pain on injection, either from drug toxicity or the fluid pressure in the interstitial tissue. Local pain has the potential to influence a user's ability to complete an injection task, resulting in a dose omission or under-dose. Also, high drug viscosity could increase the injection delivery time of the drug through the needle and increase the length of time the user must hold the injector in place (hold time) to administer the drug. The increase in hold time could reduce a user's ability to complete an injection task and result in an under-dose. The potential effect(s) of drug properties should be considered when identifying, evaluating, and managing the use-related risk for the combination product.

Q-3. How do the general definitions in the guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices* apply to a combination product?

The general definitions in the guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices* reflect HFE principles that are applicable to the combination product as a whole, and not just to the device constituent part, and may be referenced to support applying HFE to a combination product. However, for a combination product, there are two unique definitions: the final finished combination product and combination product critical task (see Q-4 and Q-5 for details).

[18] Also see the guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*.

Q-4. What is the definition of a final finished combination product?

A *final finished combination product* is the product intended for market and submitted in the marketing application. This term includes the user interface for the combination product (e.g., proposed packaging, labels and labeling, and training, if applicable).

Q-5. What is the definition of a combination product critical task and how are combination product critical tasks identified?

A *combination product critical task* is a user task which, if performed incorrectly or not performed at all, would or could cause harm to the patient or user, where harm is defined to include compromised medical care.

Although the combination product critical task definition is similar to the stand-alone device critical task definition,[19] it differs in the level of harm. Specifically, for a stand-alone device, a user task with the potential to result in serious harm is considered a critical task, and this definition remains unaltered. Also, the stand-alone drug definition of medication errors remains unchanged (see Q-1).

However, as discussed in section III, there may be use-related risks associated with the combination product as a whole that do not exist for the device alone or the drug alone. Therefore, combination product critical tasks reflect the use-related risks resulting from both the drug and device constituent parts used together as a combination product. For a combination product critical task, compromised medical care includes consideration of medication errors.[20]

A comprehensive URRA can aid in the identification of combination product critical tasks. Consistent with HFE principles, the comprehensive URRA should include a systematic evaluation of all the tasks involved in using the combination product (i.e., based on a task analysis), reflecting the use errors that may occur or the tasks that may not be completed (i.e., task failures), and the potential clinical consequences of use errors and task failures. Applicants should comprehensively consider the harm in the context of the combination product indication(s), intended use, use environment,[21] user interface, and the users.[22] The Agency is particularly interested in the assessment of tasks that directly:

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[19] Guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices,* section 3.2.

[20] See footnote 17.

[21] For the purpose of this guidance, use environment is the setting in which the product is used (e.g., home, hospital, first response) and the focus is the impact that the setting has on the user's ability to interface with the product.

[22] For additional considerations and further information regarding the URRA, see the guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices,* the guidance for industry *Safety Considerations for Product Design to Minimize Medication Errors*, and the draft guidance for industry and FDA staff *Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications* (September 2018) (when finalized this guidance will represent FDA's current thinking on this topic). FDA intends to issue additional guidance on URRAs (see PDUFA VII commitment letter).

1. Impact dosing (e.g., overdose, underdose, or missed dose), including those that may lead to lack of treatment response;

2. Impact administration of the product (e.g., wrong site of administration, improper preparation of drug/biologic before administration); or

3. Have the potential to result in harm (e.g., physical injury, adverse events, events that may need patient monitoring to confirm no harm, or events that may lead to hospitalization)

Furthermore, in their URRA, sponsors should consider whether their product may be a time sensitive or time urgent product. For time sensitive or time urgent products (e.g., emergency-use autoinjector), most or all tasks are likely combination product critical tasks because of their potential impact on delivering life-saving medication.

Once the combination product critical tasks are identified, the combination product critical tasks should be appropriately evaluated further as part of the human factors engineering process. FDA will evaluate a sponsor's identified combination product critical task list as part of the review of an HF validation study protocol. Sponsors should submit their URRA with the identification of combination product critical tasks when they submit their HF validation study protocol.[23]

The following provides hypothetical examples of some considerations for combination product critical tasks:

- Example 1- Consider an autoinjector for repeat use that includes a task to remove the cap. If a user cannot initially remove the cap, then the user is initially delayed in the sequence of tasks. However, there is no sense of urgency associated with completion of tasks for this hypothetical combination product and the user ultimately removes the cap. In cases where the timeliness of the injection is not linked to physical injury, it's unlikely that FDA would consider this task to be a combination product critical task.[24]

- Example 2 - Consider an autoinjector for a non-urgent, repeat use where the user must complete the task of pushing the needle end against the skin to activate the injection sequence and administer the dose. In this example, a user does not complete the task of pushing to activate the full injection sequence because the user did not know s/he needed to push the needle all the way down, and thus fails to administer the dose. The omission of a single dose is a medication error that may not result in an immediate change in clinical signs or symptoms; however, it is reasonable to consider the potential for repeated dose omission medication errors over the course of treatment. The treatment for

[23] For additional information see the draft guidance for industry and FDA staff *Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications*. When finalized this guidance will represent FDA's current thinking on this topic. Also, for more information on how to obtain feedback, see Q-15.

[24] Applicants should be aware that even if a task is not a combination product critical task, the collected HF data for that task may still be important in FDA's consideration of design validation (see 21 CFR 820.30(g)). In this example, if the root cause of users initially not being able to remove the cap is linked to the force specification, then FDA may further consider whether the specification has been appropriately validated.

that patient may be compromised and could result in harm to the patient. Thus, the task of pushing the needle end against the skin to activate the full injection sequence would be considered a combination product critical task.

- Example 3 - Consider a drug suspension co-packaged with a vial adaptor and an administration device that requires a task where a user must vigorously shake a powder mixed with a liquid vehicle for 60 seconds to achieve a homogenous suspension. The task of shaking vigorously for 60 seconds would be considered a combination product critical task because an inability to achieve a homogenous suspension can directly result in an improper (inaccurate) dose being administered to a patient (e.g., under or overdose medication error).

- Example 4 - Consider an on-body infusion system that can deliver a medication continuously to a patient with congestive heart disease to reduce the likelihood that the patient will be hospitalized. The patient must know how to refill the drug cartridge, apply the system to the body, activate the system, and be able to determine whether the drug is infusing and if the device constituent part is performing as expected (e.g., delivery status, refill alerts). Each of these tasks associated with the drug administration process would be considered combination product critical tasks because failure of any one of these tasks could lead to an improper dose being administered (e.g., underdose medication error). Further, such medication error could result in exacerbation of congestive heart failure that may lead to subsequent hospitalization.

- Example 5 - Consider an inhaler that requires the patient to place a drug capsule into the inhaler, where it is aerosolized for inhalation. Swallowing the capsule instead of placing it in the inhaler would be considered a medication error, even if swallowing the capsule may not cause immediate clinical signs or symptoms. It is a medication error because swallowing the capsule is an incorrect route of administration and could result in harm (i.e., non-treatment of the pulmonary disorder). The task of placing the drug capsule into the inhaler would be considered a combination product critical task.

Q-6. How does FDA evaluate HF validation study results?

From a practical perspective FDA recognizes that it may be impossible to design a user interface that is completely error-proof or risk-free, and some residual use-related risk may remain. The HF validation study results should be considered within the overall benefit-risk assessment of the combination product. All risks that remain after HF validation testing should be thoroughly analyzed by the applicant to determine whether additional modifications to the combination product user interface are warranted. FDA will evaluate the HF validation study results to determine whether the combination product user interface design has been optimized such that the use-related risks have been sufficiently reduced.[25]

[25] See also section 8.1.7, Residual Risk, in the guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices*.

Q-7. Is there a difference between the use-related risk analysis (URRA) to support the user interface and other types of risk analysis?

Yes, the URRA[26] is a subset of the full engineering risk analysis for the device constituent part and combination product as a whole (including the drug constituent part). For the purposes of this guidance, the URRA is the systematic use of available information to identify use-related hazards and to estimate the use-related risk. Additionally, the URRA should consider the intended use, as well as reasonably foreseeable misuse, and should focus on the users, use environment, user interface, and user tasks. When an applicant for a combination product is submitting a URRA, FDA recommends submitting it as a separate risk analysis and not with the full engineering risk analysis.[27]

Q-8. What considerations may apply for training as part of the user interface for combination products?

During product HFE development, a determination should be made regarding whether training will be part of the user interface. This determination should be based on an analysis of the intended users, use environments, and uses of the proposed combination product and whether training will occur consistently.[28]

Combination products are used in a variety of use environments and by different intended users, such as, hospital surgery rooms by a health care provider (HCP), emergency first responder settings by HCP, in-home procedures by HCP, and outside of a health care environment (e.g., home, schools) by patients and lay caregivers. Likewise, how training is provided varies with how the product is distributed (e.g., to a health care facility or to the patient). For products dispensed to the patient, the patient may be trained at the HCP's office (e.g., with printed materials, with a training version of the product, or with the actual product), or training may occur at the pharmacy upon patient request. Also, in some instances the user may not receive training. Furthermore, some combination products are used daily, other combination products are used intermittently (e.g., weekly, monthly) or on an as needed basis (e.g., an emergency-use injector to treat anaphylaxis). In addition, for infrequently used products, the memory of knowledge and information gained through training can decrease over time (training decay). All of these factors should be considered in determining the most appropriate training program for the combination product.

Because of the range of combination products, user interfaces, use environments, intended users, and training locations, FDA recommends HF validation training considerations such as the following:

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[26] For information on risk analysis tools such as failure mode effects analysis (FMEA) or fault tree analysis (FTA), see the guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices*.

[27] For additional information see section 6, Preliminary Analyses and Evaluations, in the guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices*.

[28] For additional information see section 8.1.4, Participant Training, in the guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices*.

- If training is part of the user interface design requirements, the training program itself should be validated. The training program validation should include the procedures used to ensure consistent and reliable training is provided for all intended users. The training program validation should also include the method for training the trainers. The combination product HF validation study submission should include the intended training program, including any repeat training, if applicable, and all materials the users are to receive with the final finished combination product.[29]

- If the training is not part of the user interface design requirements, then the combination product user interface design should support safe and effective use without training.

- If the training is optional or the provision of training cannot be ensured, then the combination product HF validation study may test both trained and untrained users to evaluate risk mitigation for both user populations. In some instances (e.g., if the untrained users are the higher risk scenario), it may be acceptable to test only untrained users.

Q-9. What is the difference between an HF actual-use validation study and an actual-use/clinical home-use study?

HF actual-use validation studies to validate the user interface may occur in circumstances when the combination product use, use environments, or other aspects are particularly complicated, poorly understood, or difficult to simulate. Also, HF actual-use validation studies may occur when simulated-use test methods are otherwise inadequate to evaluate users' interactions with the final finished combination product. Compared to the HF simulated-use validation study, the HF actual-use validation study assesses the user interface in representative patients who receive actual medical care. As with other HF studies, these HF actual-use validation studies are observed by an HF evaluator.

FDA emphasizes that the HF actual-use validation study is different from, and should not be confused with, other clinical studies that involve the actual use of the study product. Specifically, there can be different investigations of clinical safety and effectiveness of products where a clinical study participant self-administers an investigational product at home over the duration of a clinical investigation (e.g., a standalone drug oral tablet; for a combination product investigation, a drug prefilled autoinjector). These other studies have a range of different descriptive terms (e.g., phase 1, 2, 3; clinical home-use; patient handling studies; actual-use studies; open-label use; open-label safety use). In those contexts, the term "actual use" has been a source of confusion. In this guidance, FDA emphasizes that these other clinical studies have different purposes and are outside the scope of this document because they are designed to establish safety and effectiveness of the proposed product. In the studies described in this

[29] For additional information on providing information to support FDA review of the proposed training, see the draft guidance for industry and FDA staff *Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications.* When finalized this guidance will represent FDA's current thinking on this topic.

paragraph, the user interface is not observed by an HF evaluator and the studies are not HF actual-use validation studies.

In instances where an applicant may want to collect HF actual-use validation data as part of a clinical study, given the HF actual-use validation study and the clinical study have different primary objectives and endpoints, the Agency recommends that the applicant submit their proposal to the Agency for review and comment. Applicants should carefully consider whether differences in study participant training and/or supervision of study participants or other aspects of the clinical study design may negatively impact the ability of the HF actual-use data to validate the user interface.[30]

Q-10. Are there any considerations for formative HF evaluation protocols or formative HF study results?

Overall, formative[31] HF evaluations should be part of the applicant's HFE process and will play an important role in identifying user needs and how the user interface affects user interactions. HF formative evaluations are iterative throughout development; i.e., from early prototypes to the stage when the user interface of the entire combination product is finalized. Therefore, FDA generally reviews formative HF information in the following two circumstances:

- Summaries of formative HF evaluations as background information to support review of a draft HF validation study protocol.

- Formative HF evaluations as part of the overall HF process and HF report that is provided in the marketing application for a combination product. This informs FDA on how the user interface design was developed for optimization with respect to safe and effective use, as well as important outcomes of the evaluations such as understanding of user interactions and identifying combination product critical tasks.

Q-11. What HF information and/or data should be provided to support initiating clinical investigations for a combination product?

In an investigational application (IND or IDE), one of FDA's objectives in reviewing clinical investigation protocols before implementation is to help protect the rights, safety, and welfare of human subjects (subjects). Consistent with HFE principles as part of combination product development, the applicant should consider whether the risk of incorrect use or failure to perform user tasks with the combination product could cause harm to subjects. For this assessment FDA recommends the following:

[30] For additional information on HF actual-use validation studies, see the guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices*, section 8.3 (the actual use testing described in this section of the guidance is the same as the HF actual-use validation studies discussed in Q-9).
[31] For information on formative evaluations, see the guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices*, sections 3.3 and 6.4.3.

- To minimize the risk of harm in a clinical investigation, before beginning a clinical investigation, applicants should conduct a URRA in the context of the risk mitigation measures to be used in the clinical investigation.

- If the results of the applicant's URRA suggest that the use-related risks to the subjects are:

  - Acceptable (i.e., URRA results would not preclude proceeding with the clinical investigation), FDA may request the URRA if there are questions regarding safety of the subjects.

  - Unacceptable (i.e., URRA results would preclude proceeding with the clinical investigation), then before beginning the clinical investigation, the applicant should submit the URRA results and the applicant's rationale for using HF validation for purposes of a clinical investigation,[32] to demonstrate that the applicant's proposed measures adequately mitigate the risks. Assuming FDA agreement with the URRA results and agreement that HF validation is appropriate, then FDA recommends the applicant submit a draft HF validation study protocol for FDA feedback before proceeding with HF validation. Further, to assess the HF risk mitigations, FDA recommends submission of the HF study results to the IND/IDE, before beginning the clinical investigation.

In some circumstances the applicant's URRA may show that the use-related error would not result in subject harm, but could jeopardize the evaluability of the study results. In such circumstances if the applicant wishes to seek FDA's feedback, the applicant may request feedback in accordance with the procedures associated with the application type (see Q-15 for additional information regarding meeting requests with FDA).

Q-12. Does FDA expect the HF validation study that supports market authorization to be conducted at a certain development phase of the combination product?

An HF validation study is generally conducted before submission of the marketing application, once the final design of the user interface has been determined. The HF validation study report is submitted to the marketing application to support that the combination product can be used safely and effectively by intended users, for its intended uses, and in the expected use environment(s).[33] Applicants should conduct the appropriate iterative HF studies throughout the development process, but the HF validation study is generally conducted with the final finished combination product. If the HF validation study is not conducted with the final finished combination product,[34] the user interface evaluated in the HF validation study should be sufficiently representative of the user interface of the final finished combination product. In such

[32] Note, this validation is not for the purpose of the final finished combination product validation.
[33] For applicants leveraging a master file for HF data, in some instances, the master file data may suffice for one constituent part alone, but not for the combination product as a whole.
[34] For example, if it is determined that an HF validation study is needed prior to the start of a clinical investigation, as described in Q-11.

circumstances, the applicant should provide a justification for relying on the representative test product as an acceptable surrogate for the final finished combination product (also see Q-13).

Q-13. What HFE principles should be considered when modifying a combination product?

When planning a combination product design change, the URRA should include all aspects of the combination product to be modified and all elements of the combination product that may be affected by the modifications. This may occur when a manufacturer is modifying a combination product: (1) after completion of the clinical investigations to establish safety and effectiveness but before marketing authorization, (2) after an HF validation study identified unacceptable residual use-related risks, or (3) after the product is on the market. Consistent with HFE principles, whether any additional HF validation study should be conducted is based on the acceptability of the results of the URRA of the proposed modifications. In some instances, the new HF validation study may be limited in scope to evaluate those use scenarios and combination product critical tasks that are impacted by the modifications.[35]

FDA notes that the data and information needed to support a combination product design change (e.g., prefilled syringe to an autoinjector, or associated change in the drug constituent part) may involve more than an HFE assessment and such other data are beyond the scope of this document.[36]

Q-14. What are FDA review processes for combination product draft HF validation study protocols and draft labeling?

Draft HF validation study protocols will be reviewed in the time frame consistent with the lead center review program and user fee commitments or policies associated with the application type.

When labeling is submitted as part of the draft HF validation study protocol, a comprehensive labeling review will be performed by the labeling leads in each center to provide recommendations to the applicant prior to conducting the HF validation study.[37] This is done to minimize the likelihood of labeling revisions being needed after completion of the HF validation study.

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[35] For additional information on the principles of risk analysis and HF validation study of modified products, see section 8.2, Human Factors Validation Testing, in the guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices*.

[36] For additional information see the draft guidance for industry *Bridging for Drug-Device and Biologic-Device Combination Products* (December 2019). When finalized this guidance will represent FDA's current thinking on this topic.

[37] See FDA MAPP 6701.1, *Procedures for DMEPA Intra-Center Consult to DMPP on Patient-Oriented Labeling Submitted with Human Factors Validation Study Protocols*, available at https://www.fda.gov/media/131008/download.

Q-15. How do I obtain information from and provide information to FDA on my combination product HF program?

FDA encourages applicants to request early discussions with FDA regarding their HF program and the type of HF studies that might be appropriate or necessary in the planned submission. Additionally, if applicants anticipate design changes during product development before launch, FDA strongly encourages meetings during the early planning stages. Discussion topics might include how to add a new presentation to the development plan and/or how to bridge to existing data. Such discussions should provide clarity on the applicant's development plan and on FDA's recommendations and expectations for HF studies and the sequence of the development program. Where appropriate, the applicant may request HF-focused meetings for more detailed discussions.[38] For a combination product, applicants should submit meeting requests, and any other information, as appropriate, for feedback or review as discussed in this guidance, to the lead center using the process and procedures of the lead center for the application type. The meeting request should indicate that the discussion is for a combination product and request participation of all relevant centers and OCP, as appropriate.

[38] For information on requesting FDA feedback see the guidance for industry and FDA staff *Requesting FDA Feedback on Combination Products* (December 2020). For information on PDUFA submissions and meetings see the draft guidance for industry *Formal Meetings Between FDA and Sponsors or Applicants of PDUFA Products* (December 2017) (when finalized this guidance will represent FDA's current thinking on this topic). For information on requesting meetings for device application types, see the guidance for industry and FDA staff *Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program* (June 2023).