Purpose and Content of Use-Related Risk Analyses for Drugs, Biological Products, and Combination Products

Guidance for Industry and FDA Staff

DRAFT GUIDANCE

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Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Combination Products (OCP)

July 2024
Combination Products

Purpose and Content of Use-Related Risk Analyses for Drugs, Biological Products, and Combination Products

Guidance for Industry and FDA Staff

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Purpose and Content of Use-Related Risk Analyses for Drugs, Biological Products, and Combination Products 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 purpose and content of a ***use-related risk analysis***[2] (URRA) and how a URRA, along with other information, can be used to determine human factors (HF) data needs during product[3] development and to support a marketing application.[4]

This guidance applies to drug- and biologic-led combination products[5] that include a device constituent part and are the subject of an investigational new drug application (IND), a new drug application (NDA), or a biologics license application (BLA) and supplements to these

[1] This guidance has been prepared by the Divisions of Medication Error Prevention and Analysis I and II within 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 at the Food and Drug Administration.

[2] Terms that appear in bold italic type upon first use are defined in the Glossary section.

[3] For the purposes of this guidance, unless otherwise specified, the term *product* or *products* refers to drug products approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); biological products licensed under sections 351(a) and 351(k) of the Public Health Service Act (PHS Act); and combination products as identified under section 503(g)(1)(A) of the FD&C Act and approved/licensed under these sections. The term *drug* refers to a drug as defined in section 201(g)(1) of the FD&C Act (21 U.S.C. 321(g)(1)), and includes biological products as defined in section 351(i) of the PHS Act (42 U.S.C. 262(i)).

[4] This guidance is one of several documents FDA is issuing to fulfill the performance goals under the seventh authorization of the Prescription Drug User Fee Act and the third authorization of the Biosimilar User Fee Act.

[5] Combination products, as defined under 21 CFR part 3, are comprised of two or more biological product, device, or drug constituent parts (21 CFR 4.2). The term *device* refers to a device as defined in section 201(h)(1) of the FD&C Act. Combination products are assigned to a lead center for their regulation based on which constituent part provides the primary mode of action (PMOA) (21 CFR 3.4). The term *drug-led* is used to refer to combination products with a drug PMOA, which are generally assigned to CDER. Biologic-led is used to refer to combination products with a biological product PMOA, which are generally assigned to CDER or CBER. Drug or biological product led may also refer to those products assigned to CDER or CBER via the product assignment algorithm (see 21 CFR 3.4(b)). .

applications.[6] In certain cases, this guidance may also apply to the following stand-alone drug and biological products (i.e., those that are not part of a combination product):

- Human prescription drug products, including biological products, that are the subject of an IND, NDA, or BLA and supplements to these applications

- Human nonprescription drug products that are the subject of an IND or NDA, and supplements to these applications

All such products in this guidance are jointly referred to as products, and those responsible for making submissions are referred to as sponsors or applicants.[7]

This guidance does not describe the methods used to design, conduct, or analyze HF studies, how to conduct comparative analyses, or how to submit HF protocols or study results. In addition to the information described in this guidance, FDA recommends that sponsors refer to other relevant guidance documents related to product design and HF, including the following:

- Guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices* (February 2016)

- Guidance for industry *Safety Considerations for Product Design to Minimize Medication Errors* (April 2016)

- Guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)

- Guidance for industry and FDA staff *Application of Human Factors Engineering Principles for Combination Products: Questions and Answers* (September 2023)

- Draft guidance for industry and FDA staff *Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications* (October 2018)[8]

Additionally, FDA encourages sponsors to engage with FDA early in the design and development of a product to discuss the HF development program via meeting requests.

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[6] Although this guidance does not apply to medical products submitted under abbreviated new drug applications (ANDAs), an ANDA applicant may find a URRA to be a helpful tool for identifying critical tasks that may be impacted by user interface design differences and the use errors that may occur. For additional information on analyzing the user interface of a proposed generic combination product as compared to its reference listed drug, and the assessment of risks associated with any differences identified in the user interface, 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 final, this guidance will represent the current thinking of FDA. 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.

[7] For the purposes of this guidance, we use the term *sponsor* interchangeably with applicant irrespective of the particular submission type (e.g., IND, NDA, BLA).

[8] When final, this guidance will represent the FDA's current thinking on this topic.

Sponsors should refer to the appropriate guidance documents concerning meeting requests with FDA for their products and applications, including the following:

- Guidance for industry and FDA staff *Requesting FDA Feedback on Combination Products* (December 2020)
- Draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023)[9]
- Draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products* (August 2023)[109]
- Guidance for industry and review staff *Best Practices for Communication Between IND Sponsors and FDA During Drug Development* (December 2017)

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(a) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(a)), FDA licenses a biological product based on a demonstration that it is safe, pure, and potent and is manufactured in a facility designed to ensure that the product continues to be safe, pure, and potent. Section 351(k) of the PHS Act (42 U.S.C. 262(k)) provides an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed reference product.[11]

As part of FDA's evaluation of an application, FDA evaluates HF study results submitted by sponsors. This includes data to support the product user interface when submission of such data is warranted. The URRA may be used as one element in the determination of whether HF study results may be warranted as part of a new marketing application.

The URRA is a risk analysis tool used to identify use-related hazards associated with product use and the measures implemented to reduce those risks. The URRA supports the entire HF engineering process and should be considered as part of an overall risk management

[9] When final, this guidance will represent the FDA's current thinking on this topic.
[10] When final, this guidance will represent the FDA's current thinking on this topic.
[11] See also section 351(i) of the PHS Act.

framework.[12] A URRA is important to help identify use-related hazards associated with the user interface design of the combination product, as well as to characterize risks so they can be mitigated (such as through risk controls) or eliminated through improved product user interface design. The sponsor should initiate the URRA early during product development and, subsequently, use and update the URRA in all phases of the product lifecycle,[13] for example, as the product design changes, or as new risks are identified during development or post marketing.

The URRA should include the following:

- A comprehensive list of all tasks required for the use of the product
- The potential ***use errors*** and harms that may occur with those tasks
- A determination of whether each task is a ***critical task***
- Risk controls employed in the user interface design to mitigate the use errors
- Evaluation methods that have been used (or will be used) to evaluate the effectiveness of the risk controls.

The URRA, along with other information, such as comparative analyses, can help inform whether the sponsor should submit HF validation study results for Agency review as part of the marketing application. The URRA is also a key component in developing an HF validation study protocol and informing the acceptability of residual risks.[14] Additionally, the URRA may aid in demonstrating compliance with applicable requirements codified in 21 CFR part 4 subpart A for combination products.

[12] Please note that there are other considerations for developing a risk management program. For combination products that include a device constituent part, the recommendations in this guidance would serve to augment a risk management program based on International Organization for Standardization (ISO) 14971 *Application of risk management to medical devices* (2019) (ISO 14971) and the International Council for Harmonisation (ICH) guidance for industry *Q9(R1) Quality Risk Management* (May 2023) (ICH Q9(R1)). With regard to combination products, either ICH Q9(R1) or ISO 14971/ISO Technical Report (TR) 24971 *Guidance on the application of ISO 14971* (2020) (ISO TR 24971) could serve as a basis for developing a suitable framework for risk management, and reference to both can be helpful in developing such a framework. For combination products that include a device constituent part, however, FDA recommends use of an ISO 14971/ISO TR 24971-based framework, incorporating relevant considerations from ICH Q9(R1), to ensure a sufficiently robust risk management process consistent with current best practices and global regulatory trends and norms. See, for example, the Association for the Advancement of Medical Instrumentation Technical Information Report (AAMI TIR) 105:2020 *Risk Management for Combination Products* (2020).

[13] For an example about the use of a URRA to support clinical investigation protocols, see Question 11 in the guidance for industry and FDA staff *Application of Human Factors Engineering Principles for Combination Products: Questions and Answers*.

[14] See the guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices*.

III. URRA DEVELOPMENT

When developing the URRA, the sponsor should consider all the intended uses of the product, the potential product users, and the likely use environments. Each of these may impact product design, ***user tasks***, and subsequent risks and potential harms associated with use of the product. Sponsors should reference the guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices* for more details on HF and use-related risk.

The appendix includes an abbreviated example of a URRA in table format. This is one possible option for formatting a URRA and is not intended to represent the only acceptable option.

A. Identify User Tasks

A sponsor can begin the URRA process by developing a comprehensive and systematic list of all tasks involved in use of the product. This should include user tasks — those tasks related to the physical use of the product — and ***knowledge tasks*** — those tasks that involve assessing information provided by the labeling. The sponsor can identify tasks by conducting a task analysis[15] or contextual inquiry.

B. Identify Potential Use Errors

Once all tasks associated with use of the product have been identified, the sponsor should identify, for each task, what use errors can be reasonably expected to occur. Reasonably foreseeable misuse (including product use by unintended but foreseeable users) should be evaluated to the extent possible. The simplest example is task omission when a user fails to complete the task at all. Other task-related errors may be more difficult to identify; however, there are several tools that can aid in their identification such as failure modes and effects analysis or fault tree analysis.[16]

Potential use errors can also be identified from a sponsor's experience with use of the proposed product (e.g., during clinical trials), literature review, adverse event reports, or product safety communications, among other sources.

Furthermore, a sponsor can consider whether its product is similar to other marketed products with respect to device design, intended uses, users, use environment(s), and labeling. If similar marketed products exist, FDA recommends searching and analyzing data from postmarket safety databases, literature, or other sources (e.g., FDA Adverse Event Reporting System, the Vaccine Adverse Event Reporting System, Manufacturer and User Facility Device Experience, Institute for Safe Medication Practices newsletters, Anesthesia Incident Reporting System, and MedWatch) to identify known use risks associated with each potential use error.

[15] For more information on task analysis, see the guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices*.
[16] See ICH Q9(R1).

C. Identify the Potential Harms

For each potential use error, the sponsor should consider the potential harms and clinical impact. Clinical impact may vary greatly depending on the disease condition and severity, whether the medication has a narrow therapeutic index,[17] dose frequency, treatment urgency, and magnitude of potential underdose or overdose, and other factors. These and other considerations are important for understanding the clinical impact of any use errors and the acceptability of the residual risk.[18] Furthermore, the clinical impact of a use error may not be evident by a single use error. Therefore, for the clinical impact assessment, the sponsor should consider the impact for both one-time and repeated use errors (i.e., the same error occurring on subsequent use of the product). For example, in some cases, a one-time error may not have a significant clinical impact; however, repeated errors may.

D. Categorize Tasks

A URRA should categorize each task as either critical or noncritical. For combination products, "critical tasks are user tasks 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. Compromised medical care includes consideration of medication errors."[19]

E. Identify Risk Controls

For each potential use error, the sponsor should identify what risk controls are in place to either reduce or remove the risk and potential harm associated with the user interface design. For example, if a sponsor identifies during its product development that not all users recognize when there is an occlusion in the delivery line for an on-body infusion combination product, then the sponsor may implement an alarm feature as a risk control measure. The alarm should alert a user to the presence of an occlusion, which should result in the user taking an action to address the occlusion.

Sponsors can implement many possible risk controls to reduce or eliminate risks; however, generally FDA expects that sponsors focus on eliminating risks, or mitigating risks of the combination product, as appropriate, through device design when feasible rather than relying on labeling or training as risk controls. The following examples of risk controls are summarized from International Organization for Standardization (ISO) 14971,[20] and listed in priority order:

- Inherently safe design and manufacture;
- Protective measures in the product itself; and

[17] See the draft guidance for industry *Restricted Delivery Systems: Flow Restrictors for Oral Liquid Drug Products* (March 2020). When final, this guidance will represent the FDA's current thinking on this topic.
[18] A combination product critical task is defined in the guidance for industry and FDA staff *Application of Human Factors Engineering Principles for Combination Products: Questions and Answers*.
[19] Ibid.
[20] ANSI/AAMI/ISO 14971:2019 *Medical devices — Application of risk management to medical devices* (2019).

- Information for safety (such as labels and labeling) and, where appropriate, training to users.

For more information, see also the guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices*.

F. Identify Evaluation Methods

Once the risk controls have been identified, sponsors should include specific details about how they have evaluated or intend to evaluate the risk controls. For example, sponsors may indicate that a particular risk control will be evaluated as part of a specific task in the proposed human factors validation study protocol.

G. Update the URRA

The sponsor should update the URRA in all phases of the product lifecycle, for example, as the product user interface or risk controls change, or as new risks are identified during development or post marketing. For additional considerations associated with a combination product design change, FDA encourages sponsors to follow the HF principles laid out in the guidance for industry and FDA staff *Application of Human Factors Engineering Principles for Combination Products: Questions and Answers*.

IV. SUBMITTING A URRA

FDA determines HF data needs for each individual application. However, a sponsor can submit[21] a URRA along with other supportive information, such as comparative analyses, to support the position that the sponsor does not need to submit HF validation study results for Agency review in the marketing application, or to support the design of an HF validation study protocol.

A. Justifying That HF Validation Study Results Do Not Need to Be Submitted

Along with the URRA, if the same or similar combination products exist, it may be useful to conduct comparative analyses, which include a labeling comparison, a comparative task analysis, and a physical comparison between the proposed product and the comparator for the purposes of identifying what differences exist between the user interfaces and where the same or similar risks may apply to the proposed product. For certain types of applications, the use of information from another development program may require that the sponsor own the information or have a right of reference.[22] A sponsor should consider this additional information to help determine

[21] See the draft guidance for industry *Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications*. When final, this guidance will represent the FDA's current thinking on this topic.

[22] See, for example, 21 CFR 314.3, "Right of reference or use means the authority to rely upon, and otherwise use, an investigation for the purpose of obtaining approval of an application, including the ability to make available the underlying raw data from the investigation for FDA audit, if necessary."

whether the results from an HF validation study need to be submitted to support the marketing application. For the justification, the sponsor should consider multiple factors, including but not limited to intended users, uses, drug and device characteristics, dosing considerations, user familiarity and experience with product presentation, user characteristics, clinical impact of use errors, and use environment.[23]

If the sponsor determines that differences (if any) identified in the comparative analyses do not warrant submitting HF validation study results to the marketing application[24], the sponsor should submit the URRA and any other supportive information, such as comparative analyses, together with the justification for not submitting an HF validation study for review under the IND.[25]

Selecting an appropriate comparator product will depend on the regulatory pathway, and sponsors should contact the review division to ensure they are using an appropriate comparator product.[26]

B. Developing an HF Validation Study Protocol

A sponsor can use the URRA to identify the need for risk control strategies and to design an HF validation study that adequately evaluates those risk control strategies.

It is important to note that there is a connection between the tasks and risk controls in the URRA, the labels and labeling, and the HF validation study protocol. For example, critical tasks

[23] See the draft guidance for industry *Bridging for Drug-Device and Biologic-Device Combination Products* (December 2019). When final, this guidance will represent the FDA's current thinking on this topic.

[24] Separate from whether an HFVS is submitted to the marketing application, in accordance with 21 CFR part 4, a combination product that includes a device constituent part must comply with applicable quality system regulations (21 CFR part 820). This includes 21 CFR 820.30, Design controls, requirements relevant to HF testing for design verification/validation; and relevant to documentation of risk analysis. See the guidance for industry and FDA staff *Current Good Manufacturing Practice Requirements for Combination Products* (January 2017) for additional information. On Feb 2, 2024, FDA issued a final rule amending the device quality system regulation, 21 CFR part 820, to align more closely with international consensus standards for devices. FDA also made conforming amendments to 21 CFR part 4 (89 FR 7496). This final rule will take effect on Feb 2, 2026. Once in effect, this rule will amend the majority of the current requirements in part 820 and incorporate by reference the 2016 edition of the ISO 13485, *Medical devices – Quality management systems – Requirements for regulatory purposes,* in part 820. As stated in the final rule, the requirements in ISO 13485 are, when taken in totality, substantially similar to the requirements of the current part 820, 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 FD&C Act. When the final rule takes effect, FDA will also update the references to provisions in 21 CFR part 820 in this guidance to be consistent with that rule.

[25] If the sponsor intends to submit a URRA and comparative analyses to justify why an HF study does not need to be submitted for Agency review in the marketing application, FDA encourages the sponsor not to submit a protocol simultaneously. This is because the result of the URRA submission review determines whether a HF validation protocol should be submitted.

[26] As applicable, see also the draft guidance for industry *Applications Covered by Section 505(b)(2)* (December 1999), draft guidance for industry *Bridging for Drug-Device and Biologic-Device Combination Products,* guidance for industry *Determining Whether to Submit an ANDA or a 505(b)(2) Application* (May 2019), guidance for industry *Considerations in Demonstrating Interchangeability With a Reference Product* (May 2019), guidance for industry and FDA staff *Principles of Premarket Pathways for Combination Products* (January 2022), and/or the guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act* (September 2021). When final, these guidances will represent the FDA's current thinking on these topics.

identified in the URRA often use the labels and labeling as one aspect of risk control, and the sponsor should evaluate these risk controls in the HF validation study.

V. EXAMPLES

Sponsors should consider the following examples that illustrate how a URRA, along with other supporting information, as appropriate, can generally be used for determining what HF study results or information may need to be submitted to support a marketing application. These are intended as examples only, not an exhaustive list; certain products may raise distinct, product-specific considerations that are not taken into account in the examples below. If manufacturers have specific questions relating to their particular products, the Agency recommends that they contact the appropriate review division for assistance.

A. Prefilled Syringe for Use by Health Care Professionals

A sponsor is developing a drug-device combination product with a prefilled syringe (PFS) device constituent part for use by certain health care professionals (e.g., nurses) in a nonemergency health care setting. In the course of developing the URRA, the sponsor notes that the device constituent part has features that are commonly known to the intended users from other approved products and that are commonly used in the intended use environment. Further, the sponsor notes that these health care professionals have significant formal education and clinical practice experience in administering medications using this device design. The proposed PFS is a single-use device for a single dose injection where the full contents of the device are administered, not requiring weight-based dosing and administration of partial contents of the PFS for any subpopulation (e.g., pediatric).

The URRA identified all of the user tasks required to use the combination product, the potential use errors and clinical harms associated with those use errors, and the implemented risk control measures. In the sponsor's justification that no simulated-use HF validation study results need to be submitted in the marketing application, the sponsor notes that the intended users (health care professionals (e.g., nurses)) frequently perform the critical and noncritical tasks required to use the product, such as storing the product in a refrigerator, removing the air bubble, and delivering the medication subcutaneously by pinching the skin.

The sponsor submits the URRA, together with its justification for not submitting HF validation study results, to the IND for Agency review and concurrence. FDA determines, in this instance, that results of an HF validation study need not be submitted in the future marketing application.

B. Emergency Use Auto-injector for Lay Users

A sponsor is developing a prefilled drug-device combination product with an auto-injector[27] device constituent part for use in an emergency situation by lay users. In the course of developing the URRA, the sponsor notes that the device constituent part has features that may be understood by a subset of the intended user population, but that some intended users may have

[27] This particular example may also apply to other combination products for emergency use (e.g., nasal sprays).

no experience with similar products. Additionally, the sponsor notes that the conditions of the use environment may vary considerably and include several stressors (e.g., noise, distractions, stress from the emergency itself) that may negatively impact the correct use of the product. Because this is an emergency use product, incorrect use may delay treatment and cause significant harm or death to the patient.

Based on its URRA, the sponsor has identified that the use risks are such that it should submit an HF validation study in the marketing application. The sponsor proceeds by using the completed URRA to develop the HF validation study protocol, which the sponsor submits to its IND for Agency review. For this example, the Agency agrees with the sponsor's determination that results from an HF validation study should be submitted in the marketing application, and the Agency reviews and provides feedback on the HF validation study protocol.

C. Auto-injector for Lay Users — Using URRA in Conjunction With Comparative Analyses

A sponsor is developing a prefilled drug-device combination product with an auto-injector device constituent part for use by lay users in a nonemergent setting. In the course of developing the URRA, the sponsor notes that the device constituent part has user interface features that may be understood by a subset of the intended user population, but that some intended users may have no experience with similar products. Additionally, the sponsor notes that the use environments may vary considerably.

Based on its URRA, the sponsor has identified that the use risks may warrant submitting an HF validation study in the marketing application; however, the sponsor notes similarities between the design of the user interface of its proposed product and a currently approved U.S. product. Furthermore, both the proposed product and the currently approved U.S. product have similar intended users with highly similar intended user characteristics (such as age and physical and cognitive attributes, concomitant disease/conditions, and constraints or limitations), and both products are used in the same use environments. The sponsor proceeds by conducting detailed comparative analyses, including a physical comparison, task comparison, and labeling comparison. The sponsor concludes that differences identified in the comparative analyses are unlikely to impact critical tasks and use errors associated with the differences will not result in differing harms or clinical impact. The sponsor submits its URRA, comparative analyses and a justification to not submit HF validation studies to its IND for Agency review. The sponsor notes its intent to rely on the Agency's previous approval of the other product and the sponsor's

plans to submit a 505(b)(2) application.[28,29] For this example, the Agency agrees that the URRA and comparative analyses and justification are sufficient, and the sponsor does not need to submit HF validation study results to support its marketing application.

D. Drug Product With Complicated Dosing

A sponsor is developing a drug product in specially designed blister packaging intended to ensure appropriate dosage and administration by a lay user. The proposed product has a complicated dose escalation phase. The patient should take one tablet a day for the first 3 days, followed by two tablets a day for the next 2 days, and finally four tablets a day for the next 5 days. When considering the risks during early product development, the sponsor identified that if a patient deviated from the proposed dosing schedule, the potential harms include overdose that could lead to hepatotoxicity, which led to a decision to design packaging as a risk control measure. Based on the URRA, the sponsor submits an HF validation study protocol to its IND for Agency review. For this example, the Agency agrees with the sponsor's determination that results from an HF validation study should be submitted in the marketing application, and the Agency reviews and provides feedback on the HF validation study protocol.

[28] See section 505(b)(2) of the FD&C Act. There are legal and regulatory considerations that apply to 505(b)(2) applications that rely on information (for example, FDA's finding of safety and/or effectiveness for a listed drug and/or published literature) that the applicant does not own or for which it does not have a right of reference or use to support approval of a proposed product. Applicants of 505(b)(2) applications proposing to rely on such information to support approval of a proposed product should discuss their development programs with the appropriate review division in CDER's Office of New Drugs. For additional information on 505(b)(2) applications, see the draft guidance for industry *Applications Covered by Section 505(b)(2)*. When final, this guidance will represent the FDA's current thinking on this topic.

[29] Please note that this reliance approach may not be applicable under the licensure pathway under section 351(a) of the PHS Act. For information on the 351(a) or 351(k) licensure pathways, applicants should contact the appropriate review division.

GLOSSARY

For purposes of this document, the following definitions and concepts apply to use-related risk analysis (URRA). For additional information on these terms see the sections above. For related definitions see the guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices* (February 2016) and the guidance for industry and FDA staff *Application of Human Factors Engineering Principles for Combination Products: Questions and Answers* (September 2023).[1]

Critical tasks: For combination products, "user tasks 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."[2]

Knowledge tasks: Tasks that require user understanding of information provided to the user in the product's labeling and that are not typically or easily evaluated through observation of simulated use. Rather, knowledge tasks are generally evaluated through knowledge-based questions.

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

Use-related risk analysis (URRA): A risk analysis tool used to identify use-related hazards associated with medical product use and the measures implemented to reduce associated risks.

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

[1] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[2] For the critical task definition and additional information see the guidance for industry and FDA staff *Application of Human Factors Engineering Principles for Combination Products: Questions and Answers.*

396 **APPENDIX —URRA TABLE — EXAMPLE FORMAT**
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Use-Related Risk Analysis Excerpt for a Notional Autoinjector and Drug Combination Product						
Task No.	**User Task Description**	**Description of Potential Use Errors**	**Potential Hazards/Clinical Harm and Severity**	**Critical Task (Yes/No)**	**Risk Control Measure for Each Use Error**	**Evaluation Method[1]**
1	Remove pen cap by pulling.	User does not pull off cap initially.	Delay in administration of therapy (nonemergency product); however, administration of this product is not time sensitive and insignificant clinical impact expected.	No	Cross-ridge cap designed with 1-2 N pulling force (pulling force is demonstrated and confirmed by appropriate design validation).; cap removal force is consistent with other similar products for the intended user population and use environments; Cap Removal Diagram on Page ##, or Figure ### on Page ### of IFU (Instructions for Use).	Ability of user to remove cap evaluated in human factors validation study in use scenario 1: Administration of Drug, task 1.
4	Press green button to injection site and hold for 10 seconds.	Button is held for less than 10 seconds.	Full dose is not injected (underdose); may lead to decreased control of symptoms even with a single error.	Yes	IFU Step #: Press and hold the green button until click sound is heard (Page ##) of IFU.	Evaluated in human factors validation study in use scenario 1: Administration of Drug, task 4.

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[1] Some risk controls, such as low cap removal force may be evaluated by means other than human factors studies.