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WHITE PAPER

Demystifying the Use-Related Risk Analysis (URRA) in Human Factors Validation Programs

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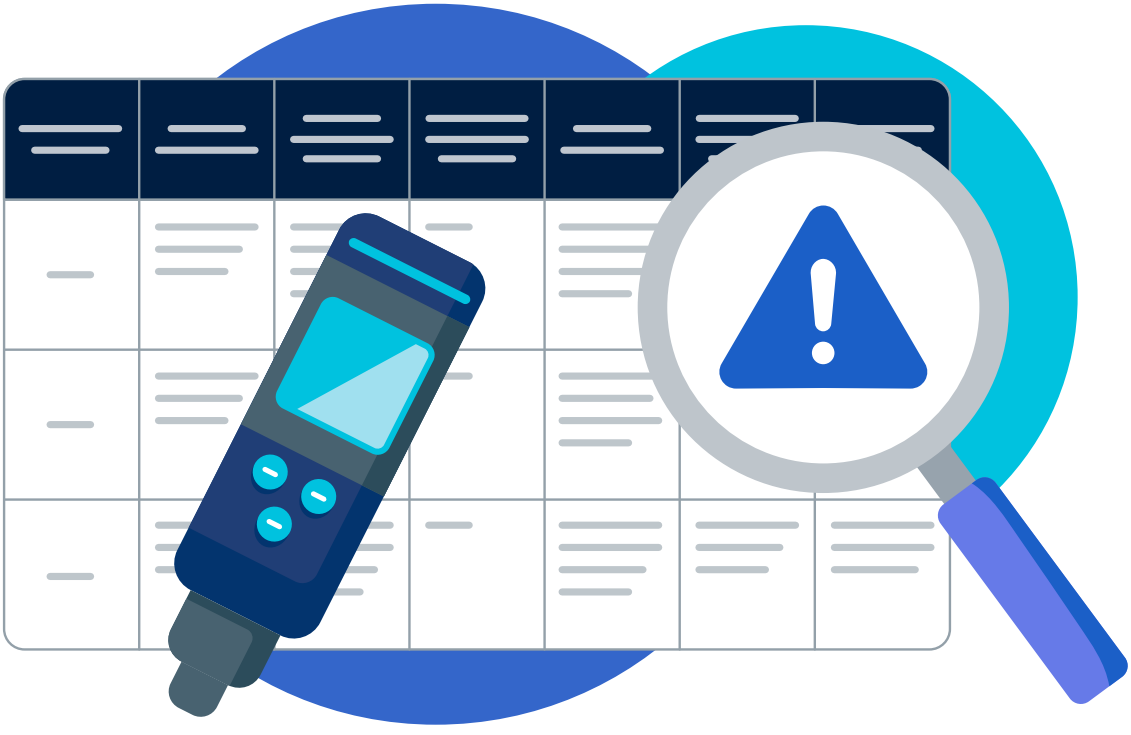

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Executive Summary

Use-related risk analysis (URRA) is a critical—but often misunderstood—component of human factors (HF) validation programs for combination drug products and medical devices. While frequently treated as a regulatory checkbox, the URRA plays a much larger role in identifying use-related risks, shaping validation strategies, and demonstrating to the FDA that those risks have been effectively mitigated.

This white paper clarifies the purpose, structure, and development of a robust URRA, with a focus on aligning with FDA expectations from both the Center for Drug Evaluation and Research (CDER) and the Center for Devices and Radiological Health (CDRH). It outlines when and how to develop the URRA across the product lifecycle, emphasizes the importance of HF-led authorship, and details how the URRA should function as a standalone document, distinct from other risk management tools.

Key considerations include:

- Building the URRA early and refining it throughout development
- Ensuring all use-related risks tied to the user interface and instructions for use (IFU) are captured and testable
- Accurately defining critical tasks and clinical harm in accordance with FDA guidance
- Using the URRA to directly inform HF validation protocols and usability improvements

Drawing on common FDA feedback and practical examples, this paper highlights frequent pitfalls such as incomplete task coverage, weak harm descriptions, and misclassification of critical tasks, while offering strategies to strengthen submissions.

It is intended for HF professionals, regulatory professionals, device engineers, product managers, and quality managers who are responsible for developing, reviewing, or supporting URRA submissions and want to better understand how to construct and apply a URRA that aligns with FDA expectations.

Ultimately, a well-developed URRA does more than support regulatory approval. It serves as a foundation for improving product safety, usability, and effectiveness by systematically identifying and addressing potential use errors before they reach the end user.

Introduction

A use-related risk analysis (URRA) document focuses on point-of-use risks for combination drug products and medical devices. Specific URRA guidance for combination drug products and biologics is provided by the Center for Drug Evaluation and Research (CDER), and medical devices are covered by guidance from the Center for Devices and Radiological Health (CDRH). The provided guidance is thorough, but experience and application of FDA feedback are the greatest teachers when developing URRAs (FDA, 2016; FDA, 2023).

The URRA is not like other risk management documents. It is specific to HF validation programs for the FDA, and that perspective must be maintained throughout its construction. However, URRA documents are often misunderstood or treated as a task to check off on the way to FDA submission. This approach can lead to gaps in risk identification and FDA feedback.

The URRA serves as a cross-check of your risk management design approach. First and foremost, it will indicate where you have vulnerability to use errors; allow it to serve as a call to action during the HF validation process. The final URRA produced should then communicate to the FDA that you have enacted specific mitigations to minimize or eliminate use errors.

When developing URRA documents, it may be tempting to map to other risk management documents and tools to maintain continuity and increase efficiency. In practice, this can create misalignment with FDA expectations if the URRA is not treated as a distinct, HF-driven analysis.

The FDA-specific URRA must be developed without strict reliance on other risk management documents due to its link to HF programs and more specifically the instructions for use (IFU). It also plays a key role in supporting marketing applications and informing appropriate human factors data requirements (FDA, 2024). This white paper explores the necessary structure and requirements for a proper URRA submission.

The Basics: What, When, and Who

The URRA covers all user interfaces, including packaging, package labeling, the device and its constituent parts, device labeling, and the IFU.

There are two stages that warrant the construction of a URRA. In early development, which may only include the device, the URRA is a useful design tool to prompt reflection on device interactions that could cause confusion or use error. It has also proven to be beneficial for de-risking clinical trials.

After the IFU is complete, the final URRA for FDA submission should be constructed. It is designed to drive the HF validation program. Note that in some cases, the URRA may be used to argue that HF validation is not needed if use errors have been mitigated to a reasonable or low level. If a study is needed, it becomes a central component to guide the validation protocol.

Given its uniqueness as a HF risk management tool, the URRA should be led and constructed by HF professionals who understand and can predict use interaction errors and routinely observe user interaction with similar devices. Development is a collaborative process as well, with sponsor involvement needed to specify harm that stems from the potential use errors identified in the URRA.

What it covers

- Packaging
- Package labeling
- The device
- Device labeling
- Instructions for use (IFU)

When to build it

Stage 1: Early development

- → Design tool for reflection
- → May cover device only
- → Prompts reflection on use errors and de-risks clinical trials

Stage 2: After IFU completion

- → Final URRA for FDA submission
- → Drives HF validation program
- → May argue validation not needed or guides validation protocol

Who builds it

HF professionals

- → Lead and construct the URRA
- → Predict use interaction errors
- → Observe users with similar devices

Sponsor / device maker

- → Collaborative involvement required
- → Specifies harms stemming from potential use errors identified

How to Construct the URRA

The URRA should be completed as a standalone document and as part of a validation protocol. CDER and CDRH both require URRAs, but there are some differences to note depending on whether the product is a combination drug product or a medical device.

Combination Drug Products

The IFU and URRA are created in conjunction with one another. Required tasks and potential or likely use errors need to be identified and included in the IFU.

Once the IFU is created and optimized for usability, the URRA is completed with a focus on covering every statement in the IFU, which is a CDER requirement for all combination products (FDA, 2016).

The two documents influence one another, so it is beneficial to start the URRA prior to completing the IFU as it will help optimize the final IFU.

When creating the URRA table for combination products, be sure to follow specific FDA guidelines for required column headers:

1. Task Number
2. User Task Description
3. Description of Potential Use Errors
4. Potential Hazards / Clinical Harm and Severity
5. Critical Task (Yes/No)
6. Risk Control Measure for Each Use Error
7. Evaluation Method

All but two columns, Potential Hazards/Clinical Harm and Severity, Critical Task (Yes/No), will be completed by the HF team. The information needed for completion can be found in the IFU and the validation protocol. The sponsor or client will fill out the remaining two items.

Careful guidance from the HF team is required here as the FDA stipulates specific content in those columns, with Critical Task having a separate definition for combination products and medical devices.

1. Task Number

Task Number is deceptively simple and one of the most common stumbling blocks. The task number is a unique identifier assigned to each task listed in the table. It enables traceability across documentation and helps reviewers quickly reference specific items.

HF teams must remember that it is not associated with step numbers in the IFU or individual use errors. It will also not match other documentation, such as a Failure Modes and Effects Analysis (FMEA) or Use Failure Mode and Effects Analysis (UFMEA). The task number only exists to number user tasks within the URRA table and act as a locating or reference point for the table.

2. User Task Description

User Task Description houses a comprehensive list of tasks involved in the use of the product—both physical use and knowledge tasks. It is important to always phrase tasks in the positive; tasks should never begin with, “Does not…”. User tasks listed in the URRA may not directly correspond to the steps described in the IFU, as steps in an IFU may have multiple actions, and each user action in the IFU should be listed individually.

3. Description of Potential Use Errors

Description of Potential Use Errors lists reasonably foreseeable misuse by all potential users, including misuse by those who are not the intended user. Some potential use errors might not be recognized until the HF validation testing is conducted, which is why the test protocol should include mechanisms to detect previously unanticipated use errors. Then, the URRA can be updated as needed.

The URRA should include use errors to cover every statement in the IFU for a combination product. This includes all actions or tasks, interactions with packaging or other items, storage, disposal, repeated use, important warnings, cautions, and "do not" statements. During validation testing, all use errors should be tested either by an observational task or a knowledge task.

If there is a use error that doesn't make sense or is difficult to observe during testing, consider whether it truly needs to be included in the IFU. If it is removed from the IFU, it can then be removed from the URRA. Also, be sure not to include patient or prescribing information in the IFU or URRA for a combination product, as that information will stay in the patient information insert.

Example: Defining a Use Error

Consider the following example involving a pre-filled syringe. Inside the IFU, you see this statement: "Do not touch the plunger head while inserting the needle into the skin." Would it make sense to list the error in the table as "Touches the plunger head while inserting the needle into the skin?"

At this point, further questioning is needed to determine whether simply touching the plunger head results in hazard or harm that must be avoided. Ask why the "do not" statement exists in the IFU; there is often potential to get more specific and target the real use error associated with the statement. After considering this, it may be determined that the "do not" statement was included to prevent premature expulsion of medicine when handling the syringe. In this case, a better use error statement would be, "Prematurely presses down the plunger head while inserting the needle into the skin, resulting in a loss of medicine." This statement would only result in a use error if the drug were actually expelled, which is what the instruction intends to avoid.

The initial version of this user task would result in a recordable error every time a user touched the plunger, even if none of the drug was expelled. Greater clarity in the user task helps prevent skewed results during validation testing.

User Task Description	Description of Potential Use Errors
Remove Syringe from Refrigerator	Does not remove syringe from refrigerator
Allow to Warm to Room Temperature	Does not allow the syringe to warm to room temperature (sit for approximately 30 minutes)
Check Drug Name	Does not check drug name
	Uses incorrect drug
Check Appearance of Medicine	Does not check appearance of the medicine in the syringe
	Does not know the medicine should be clear to slightly yellow
	Uses syringe if the medicine is cloudy, discolored, or contains flakes or particles

4. Potential Hazards / Clinical Harm and Severity

Potential Hazards/Clinical Harm and Severity is the first column to be filled out in conjunction with the sponsor. It includes potential hazards associated with user performance, the conditions that could lead to those hazards, and the resulting clinical harm (the negative outcome to a patient or user if a use error occurs).

For each use error, include both the hazard and the harm in the FDA-specified format of listed hazard/clinical harm (e.g., Delayed or no dose/Minor or no reduction in therapeutic benefit). Specific information for both elements is desirable, but the FDA will primarily be concerned with clinical harm when evaluating use errors and the URRA as a whole. Expect the majority of feedback to focus on clinical harm.

While the term "severity" is included, the meaning for combination products differs from medical devices. Logic would indicate that this information could be taken from the FMEA or the severity level/rating included in the medical device URRA, but that is not the intent. In this specific context, the FDA prefers a small amount of detail to describe how each hazard will harm the patient. For example, instead of only listing skin irritation or rash as the clinical harm, specify a serious rash leading to open sores and chance of infection.

Regarding frequency, FDA guidance states, "… consider the impact for both one-time and repeated use errors (i.e., the same error occurring on subsequent use of the product)." In a combination product URRA, this means a combined hazard/harm entry that covers both one-time and repeated use, not multiple hazard/harm entries (FDA, 2016).

5. Critical Task

Critical Task has a different definition for combination products and medical devices, and those definitions will not correlate with criticality for other documentation, such as the FMEA. In the case of combination products, critical tasks are defined as "a user task that, 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." FDA guidance states, for a combination product critical task, "compromised medical care includes consideration of medication errors" (FDA, 2024).

Compromised medical care includes any dosing error, no matter how insignificant, meaning any hazard or harm related to a dosing error is considered critical. Note that a delay of dose is only considered critical if the medication is time-sensitive (e.g., insulin). This definition results in nearly all user tasks in the URRA being critical for most combination drug products.

6. Risk Control Measure for Each Use Error

Risk Control Measure for Each Use Error describes the risk controls in place for each potential use error to reduce or remove the risk and potential harm associated with the user interface design. Risk control measures or mitigations can include items related to:

- Device design
- IFU and other instructional materials
- Package labeling or design
- Training
- Specific user population experience or prior training
- Sponsor planned support or interventions

Note that training should only be included if it is a significant part of the planned user interaction. It will then need to be part of validation testing, along with a worst-case scenario where training is not included.

7. Evaluation Method

Evaluation Method contains specific details about each use error evaluated during the validation study. This is done to determine that the intended users can safely and effectively perform the task and that mitigations are acceptable. The FDA segregates evaluation methods into both observational tasks and knowledge tasks, so each item should be listed under the appropriate category to indicate how it will be approached during validation testing.

Medical Devices

URRAs for medical devices have several differences when compared to those for combination devices. The main differences include changes to the columns included in the table and changes to the names of some of the column headers (FDA, 2026). The table columns for a medical device URRA include:

1. Task ID
2. User Task
3. Possible Use Error(s)
4. Hazardous Situation
5. Potential Harm to Patient/Operator
6. Severity of Harm
7. Critical Task (Y/N)
8. Risk Control Measure(s)
9. Validation Method for Effectiveness of Risk Control Measure

Unlike combination products, the severity of harm column in a medical device URRA is meant to indicate the level of harm. Guidance on the definition of harm is flexible but referencing the ISO 14971 standard of 2018 is recommended (ISO, 2018). The level of harm may also be related to an existing FMEA or Fault Tree Analysis (FTA).

The critical task definition will still differ from the FMEA, so be sure to apply the correct guidelines. CDER and CDRH provide very similar definitions for critical task, but there is one specific difference. For medical devices, CDRH adds the term "serious." Use errors that could cause minor harm, such as discomfort, are not considered critical.

Medical device URRAs are also not required to include every statement provided in the device's IFU or user manual. All actions or tasks, user responses to each category of alarm, and a representative selection of caution and warning statements must be incorporated into the completed URRA. If an element will be measured during the validation study, it should be included.

Task ID	User Task	Potential Use Error(s)	Hazardous Situation	Potential Harm to Patient/ Operator	Severity of Harm	Critical Task (Y/N)	Risk Control Measure(s)	Validation Method for Effectiveness of Risk Control Measure
Task #	Charge device before use	Does not charge device before use	Device interruption of power during use, incomplete therapy	Sudden loss of treatment, insufficient output, and symptom increase	Serious	Y	**Device Design:** ▪ Charger provided with product ▪ Charging port on side of device clearly marked	**Observational Tasks:** ▪ Participants will be observed as to whether they charge the device for 10 minutes prior to use

CDER (Combination Drug Product)

"User tasks that, 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."

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

CDRH (Medical Device)

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

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

Common FDA Feedback

Comprehensiveness of URRA

The FDA is concerned with comprehensiveness, particularly for combination drug products (FDA, 2016; FDA, 2023). All tasks, warnings, and precautions in the IFU must be included. Below are examples with additional information to illustrate:

> "Your URRA is incomplete because it does not comprehensively evaluate all tasks, warnings, and precautions in the instructions for use (IFU)."

> "We are concerned that all use-related failure modes and associated risks have not been identified for your proposed product."

The second statement concerns inclusion of all potential failure modes and associated risks. For example, a product is dosed twice daily, and the only failure mode listed is the patient dosing more than twice daily. The FDA will also request covering a failure mode of dosing less than twice per day.

> "Your URRA does not include a comprehensive description of the clinical impact of potential use errors."

> "It is unclear what the actual clinical consequence and severity of harm is based on this description."

This refers to clinical impact, including significant description and granularity. Example: A nasal spray is intended for the nose. The use error listed is the user spraying in the eyes or mouth. When listed as the harm, this provides insufficient information. The impact must be included, whether that is minor irritation or a severe clinical consequence.

> "Your URRA does not appropriately categorize some tasks as critical. For example, the task 'Clean Injection Site' and 'warm to room temperature' are categorized as a non-critical task. However, per your URRA, the potential harms identified suggest these are critical tasks."

All tasks that the FDA considers critical must be listed as such.

Negative Transfer

Negative transfer is an additional source of error that is not necessarily a task or derived directly from the IFU. In cases where a sponsor introduces a new device for an existing drug, the agency's concern turns to negative transfer between the old and new devices. The FDA requires that this be pointed out separately with its own row in the URRA.

The concern is that users of the current device may have negative transfer to the new device. How are those use errors being mitigated? Reliance on device intuitiveness, adding a quick reference guide, or sending letters to patients explaining the changeover are potential mitigations.

URRA Approach by Sponsor

Reducing critical tasks or risks may seem appealing, but downplaying significance is counterproductive. The FDA does not base its evaluation purely on risks; it also weighs usability. For example, consider the device packaging for a combination drug product with an auto-injector. The first step of product use requires removing it from the carton. The task may be listed as non-critical or low risk, since potential harm is minimal, downplaying the significance in the URRA.

However, during the validation study, roughly half the participants struggle to open the carton. Ultimately, the FDA will take issue with that. Requested redesign of the carton and a new validation study for that task are probable. The lesson learned is that if you demonstrate poor usability that leads to use errors, the risk associated with this task won't really matter.

Nearly all tasks for a combination drug product should be critical. Listing tasks as less critical or risky may raise the interest of the FDA, prompting further inquiry and investigation. Another word of caution: Never say "reverts to current standard of care" as risk mitigation. This indicates that the intended design failed and will not be acceptable to the FDA.

Risk Management Reconciliation

Consistency is desirable across risk management documents and analyses, but the URRA is a unique document in the HF process. Although it can provide some influence on other risk management resources, the reverse is not true. The URRA cannot be altered in format or information, and it does not contain a Risk Priority Number (RPN). Its focus on point-of-use risk purposely excludes other sources of error or failure that are captured elsewhere.

Lifecycle Management

The URRA is a living document. Potential use errors and risks should be revised as new information is uncovered through clinical trials and formative studies. Mitigations should be revised as well. Finding new ways to minimize the potential use errors is the true focus when progressing through development and the HF program.

Winning Strategies

- Consider carefully what is truly an error or risk.
- Instruct tasks so that use errors are less likely. For example, asking users to estimate time accurately frequently fails. Instructing the user to hold something down for 10 seconds will result in each individual holding for a different amount of time. No one will truly be aware when 10 seconds transpires. However, instructing users to count to 10 has a much greater chance of success.
- Reflect in the URRA that some tasks can have either-or properties to avoid unnecessary use errors. For example, perhaps releasing a pinch after pinching and inserting a needle doesn't matter. Keeping or releasing the pinch has the same risk.
- Create the URRA early and iterate it often.
- Base the final URRA on the final IFU.
- Ensure that all potential use errors are written in a way that they can be evaluated and measured in the HF validation study.
- Do not ignore "non-critical" or "low risk" tasks in the HF program.
- Let the URRA guide you to creating a safer, more effective, and more usable product.
- The submitted URRA should show your strengths, not your weaknesses.

Conclusion

Proper URRA submissions require attention to structure and requirements without reliance on other risk management documents. However, many organizations struggle to apply these expectations in practice, often treating the URRA as a documentation exercise rather than a tool to guide risk identification and validation strategy. The final submitted version must communicate to the FDA that mitigations are in place to minimize or eliminate use errors.

The URRA's tie to HF programs makes it a unique tool to cross-check the risk management design approach, uncovering vulnerabilities to use errors in both combination drug products and medical devices. When developed early, led by HF expertise, and iterated throughout development, the URRA helps close common gaps in risk identification and ensures alignment between intended use, user behavior, and validation outcomes. Maintaining that HF emphasis during URRA construction is key to maximizing benefit and document accuracy.

Developing thorough URRAs can be challenging, but experience and application of FDA feedback offer great opportunities for learning and process improvement. Organizations that refine their approach over time—using the URRA as an active input into design and validation rather than a downstream deliverable—are better positioned to reduce regulatory friction and strengthen submission quality. Remember, the URRA is more than another checkpoint on the road to validation. It is a guide to improved safety, efficacy, and usability.

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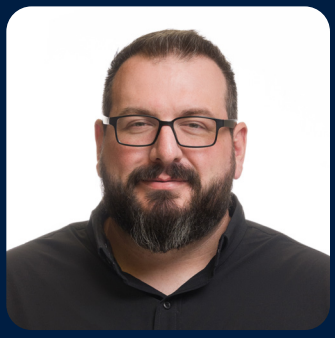

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Dr. Andre and his staff have been at the forefront of the combination drug product and medical device Human Factors movement, having managed and executed hundreds of HF validation programs for pharma, biotech, and medical device sponsors all over the world. IAA's 33 years of healthcare human factors experience is incomparable. Dr. Andre has provided human factors training to the FDA reviewers, and for 10 years moderated an annual FDA-Industry human factors workshop.

About Interface Analysis Associates

Interface Analysis Associates (IAA) is a human factors engineering and usability consulting firm specializing in medical devices, combination drug products, and other regulated technologies. Since 1993, IAA has supported product development and regulatory programs through user-centered research, usability testing, and risk analysis, helping organizations improve safety, usability, and overall product performance. Learn more at interfaceanalysis.com.