05 September 2024

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
via online submission to https://www.regulations.gov/

RE: Docket No.**FDA-2024-D-2484 "Purpose and Content of Use Related Risk Analyses for Drugs, Biological Products, and Combination Products"**

Dear Sir or Madam,

The International Society for Pharmaceutical Engineering (ISPE) appreciates the opportunity to comment on the above-referenced draft guidance.

ISPE acknowledges the value of the Use Related Risk Analyses for Drugs, Biological Products, and Combination Products Guidance for Industry. However, this guidance introduces terms defined in IEC/ISO standards but not in this document. For clarity, ISPE recommends that these terms be added to the Glossary.

ISPE is a not-for-profit organization of individual members from pharmaceutical companies, contract manufacturing organizations, suppliers and service providers, and health authorities. The 22,000+ members of ISPE lead scientific, technical, and regulatory advancement throughout the entire pharmaceutical lifecycle in more than 90 countries around the world. ISPE does not take a political position or engage in lobbying activities or legislative agendas.

We appreciate the opportunity to submit these comments for your consideration. Please do not hesitate to contact me if you have any questions.

Respectfully,

Thomas B. Hartman
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cc: Scott Billman, ISPE Board Chair

Response to a request for comments **Docket No.FDA-2024-D-2484** "Purpose and Content of Use Related Risk Analyses for Drugs, Biological Products, and Combination Products "

Comments submitted by the International Society for Pharmaceutical Engineering (ISPE), regulatorycomments@ispe.org

GENERAL COMMENTS ON THE DOCUMENT
Overall, this guidance does not include specific examples to address having human factors (HF) validation completion prior to/for the investigational new drug (IND) as described in FDA's guidance, *Application of Human Factors Engineering Principles for Combination Products: Questions and Answers; Guidance for Industry and FDA Staff* (September 2023). ISPE recommends that FDA align this guidance document with the FDA guidance "Application of Human Factors Engineering Principles for Combination Products: Questions and Answers; Guidance for Industry and FDA Staff".
ISPE recommends harmonizing terminology throughout the guidance with ISO 14971 as per FDA's recommendation in Footnote 12 to utilize this standard. There are several examples in this guidance where the terms and definitions do not align with this international standard. Refer to specific ISPE comments on the text that follow.

Specific Comments on the Text

ISPE indicates text proposed for deletion with ~~strikethrough~~ and text proposed for addition with **bold and underlining**.

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Section or Line Number	Current Text	Proposed Change	Rationale or Comment
Lines 95-96	The URRA may be used as one element in the determination of whether HF study results may be	The URRA may be used as one element in the determination of whether HF study results may be warranted as part of a new	The URRA can be used as part of both a new marketing application and IND application. This additional language would align with the FDA guidance,

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	warranted as part of a new marketing application.	marketing application or for an investigational new drug (IND) application.	*Application of Human Factors Engineering Principles for Combination Products: Questions and Answers; Guidance for Industry and FDA Staff* (September 2023), which describes using a URRA to determine if HF testing is needed to enable clinical investigations for combination products in question Q-11.
Lines 101-102	A URRA is important to help identify use-related hazards associated with the user interface design of the combination product…	A URRA is important to help identify use-related ~~hazards~~ hazardous situations associated with the user interface design of the combination product…	Replace "hazards" with "hazardous situations" as per ISO 14971 definitions. Given the recommendation to utilize ISO 14971 in footnote 12, ISPE recommends harmonizing terminology with ISO 14971 so as not to create confusion. Refer to Annex C, Fundamental risk concepts, in ISO 14971 for further information on how hazards vs. hazardous situations are defined.
Lines 131-132	When developing the URRA, the sponsor should consider all the intended uses of the product, the potential product users, and the likely use environments.	When developing the URRA, the sponsor should consider all the intended uses of the product, the ~~potential~~ intended product users, and the likely use environments.	The focus of the URRA should be on intended product users rather than "potential" product users.
Lines 143-145	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 or contextual inquiry.	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	The term "knowledge task" is not correct terminology in the context of a task analysis. Knowledge tasks are not user tasks as they are not described in a task analysis but are assessment methods used to confirm effectiveness of risk mitigations in the labeling. These "knowledge tasks" cannot already be defined in the task analysis since the

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		conducting a task analysis or contextual inquiry.	information to be provided in the labeling is only defined later in the URRA, i.e., at a later step. If the proposed change is not implemented, ISPE recommends that this section of the guidance be clarified as the current text is ambiguous. The current text seems to say that knowledge tasks (KTs) are identified through task analysis. However, commonly knowledge task assessment (KTA) questions are identified after a Risk Analysis reveals that some risks need to be mitigated by labeling with warning and caution statements. As such, KTs are only indirectly identified through task analysis and directly through risk analysis.
Lines 151-152	Reasonably foreseeable misuse (including product use by unintended but foreseeable users) should be evaluated to the extent possible.		This guidance introduces terms that are defined in IEC/ISO standards but are not defined in this document. For clarity, ISPE recommends that these terms be added to the Glossary starting on line 370. For example, the term “Reasonably Foreseeable Misuse” is a defined term in ISO 14971 and includes both Use Error and Abnormal Use (reckless and deliberate misuse, e.g., sabotage). International standards such as IEC 62366-1:2015 exclude Abnormal Use because it is beyond reasonable control

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			by a manufacturer. Because of this, IEC 62366-1 does not use the term Reasonably Foreseeable Misuse, since it can cause confusion in human factors engineering/usability engineering (HFE/UE) analysis. ISPE recommends that DA consider removing the term or, if it is kept, to note that Abnormal Use is considered part of this term but a manufacturer is not expected to mitigate Abnormal Use. ISPE also recommends adding both terms "Reasonably Foreseeable Misuse" and "Abnormal Use" to the glossary.
Lines 225- 230	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."	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. If the URRA update identifies new use error or harm, HF testing to evaluate potential mitigations should be considered.	ISPE recommends including a revaluation of human factor testing if a new unknown use error or harm was identified during the product lifecycle, post-marketing, or lifecycle management phase. URRA updates may trigger new Human Factor assessments if a new or unknown use error or harm is identified during the product lifecycle. A combination of product design changes may also trigger HF assessments, emphasizing reevaluation.
Section IV, Footnote 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	Delete text and replace with language from Lines 273-280 in FDA draft guidance, *Content of Human Factors Information in*	The FDA's draft language in footnote 24 is confusing and could be interpreted as stating that a human factors validation study is always required to comply with

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	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,	*Medical Device Marketing Submissions; Draft Guidance for Industry and Food and Drug Administration Staff* (December 2022): The Quality System Regulation (21 CFR part 820) requires that manufacturers of certain finished devices verify and validate device design, review and approve changes to device design, and document changes and approvals in the design history file (21 CFR 820.30). FDA recommends that human factors information be maintained by the manufacturer regardless of whether it is submitted to FDA. Manufacturers must keep records to the extent required under applicable law, including the Quality System Regulation (e.g., 21 CFR 820.30(j)), and these (and other) records must generally be made available to an FDA investigator upon request (see section 704(e) of the Federal Food, Drug, and Cosmetic Act).	21 CFR 820.30, irrespective of other means of providing objective evidence that the device conforms to defined user needs and including situations where FDA approves a product without requiring an HFVS via the methods described in this guidance. This is an incorrect interpretation of design validation regulation and conflicts with the human factors analysis methods FDA is promoting within this guidance. Conducting a URRA and appropriate additional analyses (e.g., risk, comparative, etc.) and concluding that no additional data are needed, is a form of objective evidence and is design validation. In situations where FDA approves a premarket application on the basis of URRA and other analytical information, means FDA has determined that the device (including its user interface), is acceptably safe and effective. ISPE also notes that footnote 24 is inconsistent with the approach taken in FDA's draft guidance *Content of Human Factors Information in Medical Device Marketing Submissions; Draft Guidance for Industry and Food and Drug Administration Staff* (December 2022). While the scope of these two guidances are different (e.g., combination product

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	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.		submissions vs. medical device submissions), the underlying regulations governing the device constituents and medical devices are the same. Therefore, ISPE recommends FDA align the regulatory standards between these two guidances. This could be accomplished by replacing footnote 24 with the text from Line 273-280 in the *Content of Human Factors Information in Medical Device Marketing Submissions; Draft Guidance for Industry and Food and Drug Administration Staff* (December 2022). ISPE also notes that the current text introduces the term HFVS which is not defined or used elsewhere in the document. Using ISPE's proposed text does not include this term.
Lines 323- 328	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	ISPE recommends adding a footnote to cross-reference FDA guidance, *Application of Human Factors Engineering Principles for Combination Products: Questions and Answers; Guidance for Industry and FDA Staff* (September 2023) regarding critical task identification for emergency use products. For time sensitive or time urgent products (e.g.,	Consistent language with FDA's guidance, *Application of Human Factors Engineering Principles for Combination Products: Questions and Answers; Guidance for Industry and FDA Staff* (September 2023), specifically for emergency-use products, is needed for critical task categorization. This footnote will reemphasize that most or all tasks are likely combination product critical tasks for time-sensitive or time-urgent

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	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.	emergency-use autoinjector), most or all tasks are likely combination product critical tasks because of their potential impact on delivering life-saving medication.	products (e.g., emergency-use autoinjector) because of their potential impact on delivering life-saving medication.
Lines 383-386	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.	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~~ implemented in a study as knowledge-based questions.	ISPE suggests amending the wording to reflect that "knowledge tasks" are a tool to check whether the user has understood the labeling information provided and is thus tested as part of a HF study. The "knowledge tasks" included in such a study should be selected using a risk-based approach, focusing on criticality.
Lines 388-390	Use error: User action or lack of action that was different from that expected by the manufacturer and causes 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 error: User action or lack of action that was different from that expected by the manufacturer and causes a result that (1) was different from the result expected~~,~~ and (2) was not causes solely by device failure~~., and (3) did or could result in harm.~~	This definition of Use Error does not agree with international standards, where IEC/ISO definitions do not mention Harm at all. A use error is a mistake. It may or may not lead to harm, but that consequence is determined by risk analysis e.g., URRA. A subsequent result in harm is not relevant. ISPE recommends removing clause 3 of the definition in the guidance to better align with international definitions.
Lines 392-393	Use-related risk analysis (URRA): A risk analysis tool used to identify use-related hazards associated with medical product use and the measures	Use-related risk analysis (URRA): A risk analysis tool used to identify use-related ~~hazards~~ hazardous situations associated with medical product use and the measures	Replace "hazards" with "hazardous situations" as per ISO 14971 definitions. Given the recommendation to utilize ISO 14971 in footnote 12, ISPE recommends harmonizing terminology

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	implemented to reduce associated risks.	implemented to reduce associated risks.	with ISO 14971 so as not to create confusion.
Appendix – URRA Table – Example Format – "Potential Hazards/Clinical Harm and Severity"	Potential Hazards/Clinical Harm and Severity	Table Header – "Potential ~~Hazards~~ Hazardous Situation/Clinical Harm and Severity"	Replace "hazards" with "hazardous situations" as per ISO 14971 definitions. Given the recommendation to utilize ISO 14971 in footnote 12, ISPE recommends harmonizing terminology with ISO 14971 so as not to create confusion.
Appendix – URRA Table – Example Format – "Potential Hazards/Clinical Harm and Severity" – Task 1	Delay in administration of therapy (nonemergency product); however, administration of this product is not time sensitive and insignificant clinical impact expected.		This example does not include a description of the harm. Severity is only indirectly characterized as "insignificant clinical impact". It is also not clear why the word "expected" is included, as this relates to the idea of probability of occurrence, which FDA HF guidance has up until now rejected. ISPE recommends the example be structured in a way that more clearly corresponds with the column headings to minimize confusion among practitioners who will try to use the guidance. Harm and severity should be clearly described in the examples.
Appendix – URRA Table – Example Format – "Critical Task	Critical Task – "No"		While intuitively it makes sense that difficulty removing the cap - especially an initial difficulty - should not be a critical task, it is not clear from this example how this could be determined because there is no description of the

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(Yes/No)" – Task 1			harm. ISPE recommends clarifying the example (e.g., specifying that the use error does not result in any harm) so that practitioners trying to use the guidance can clearly link these examples to the concepts covered in the body of the guidance doc.
Appendix – URRA Table – Example Format – "Risk Control Measure for Each Use Error" – Task 1	Cross-ridge cap designed with 1-2 N pulling force (pulling force is demonstrated and confirmed by appropriate design validation), …	Cross-ridge cap designed with 1-2 N pulling force (pulling force is demonstrated and confirmed by appropriate design ~~validation~~ verification.	Cap removal force should be demonstrated via design verification, not design validation, as it is a design requirement, not a user need requirement. Verification is used to evaluate design requirements; validation is used to evaluate user needs. Cap removal force is a design requirement.
Appendix – URRA Table – Example Format – "Risk Control Measure for Each Use Error" – Task 1	…cap removal force is consistent with other similar products for the intended user population and use environments…	~~…~~cap removal force is consistent with data available to the sponsor from other similar products for the intended user population and use environments…	ISPE recommends modifying this sentence. A given manufacturer will likely not have access to verification data for products manufactured by other manufacturers.
Appendix – URRA Table – Example Format – "Evaluation Method" – Task 1	Ability of user to remove cap evaluated in human factors validation study in use scenario 1: Administration of Drug, task 1.	Ability of ~~user~~ participant to remove cap evaluated in human factors validation study in use scenario 1: Administration of Drug, task 1.	Accepted industry best practice is to refer to individuals who participate in HF studies as "participants." Participants are the small "sample" of the larger "population" of "users". The performance of the sample of "participants" in HF studies is used to generalize and make conclusions about how the population of "users" will use

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			the product once marketed. Only individuals who actually use the medical product should be referred to as "users."
Appendix – URRA Table – Example Format – “User Task Description” – Task 4	Press green button to injection site and hold for 10 seconds.	Press green button and hold the autoinjector in place for 10 seconds.	Because the URRA example in the Appendix is incomplete, i.e., goes from Task 1 to Task 4, this statement is unclear and could have various interpretations. The additional proposed text provides clarity for the specific task addressed in “Task 4”. It is assumed that a previous task would refer to the user holding the autoinjector to the injection site.
Appendix – URRA Table – Example Format – “Potential Hazards/Clinical Harm and Severity” – Task 4	Full dose is not injected (underdose); may lead to decreased control of symptoms even with a single error.		Severity of harm is not described in this example. ISPE recommends including a description of harm to align with the column heading.