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IPAC-RS Comments on FDA Draft Guidance: "*Purpose and Content of Use-Related Risk Analyses for Drugs, Biological Products, and Combination Products - Guidance for Industry and FDA Staff*"[1]

The International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS) is an international association of companies focusing on orally inhaled and intranasal products. Member companies of IPAC-RS develop, manufacture and market both brand-name and generic products (see the list of members at https://www.ipacrs.org/about).

IPAC-RS seeks to advance the science, and especially the regulatory science, through joint research, consensus building, development of best practices, and collaborations among stakeholders. As such, IPAC-RS appreciates FDA's publication of the draft guidance "*Purpose and Content of Use-Related Risk Analyses for Drugs, Biological Products, and Combination Products - Guidance for Industry and FDA Staff*", and would like to suggest the following comments.

General Comments

1. Please align the content of this draft guidance with other guidance documents issued by FDA. For example, see below the differences between this draft guidance and the *"Content of Human Factors Information in Medical Device Marketing Submissions Draft Guidance for Industry and Food and Drug Administration Staff" (December 2022*). Please clarify FDA expectations, or explain why there are two different approaches for URRA Format and Content for drug-device combination products in CDER--led applications.

Medical Devices	**Combination Products**
"Content of Human Factors Information in Medical Device Marketing Submissions Draft Guidance for Industry and FDA Staff", December 2022, CDRH (https://www.fda.gov/media/163694/download)	*"Purpose and Content of Use-Related Risk Analyses for Drugs, Biological Products, and Combination Products - Guidance for Industry and FDA Staff",* July 2024, CDER/CBER/CDRH/OCP (https://www.fda.gov/media/179858/download)

[1] Purpose and Content of Use-Related Risk Analyses for Drugs, Biological Products, and Combination Products | FDA CDER/CBER/CDRH/OCP July 2024

263 **Table 2. Example tabular format for the use-related risk analysis**

Use-related risk analysis Task #	User Task	Possible use error(s)	Potential hazards and clinical harm	Severity of harm	Critical Task (Y/N)	Risk Mitigation Measure(s)[25]	Validation method for effectiveness of risk mitigation measure[26]
Task #1							
Task #2							

264

396 **APPENDIX —URRA TABLE — EXAMPLE FORMAT**
397

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]**
	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	No	Cross-ridge cap designed with 1-2 N pulling force (pulling force is demonstrated and confirmed by appropriate design	Ability of user to remove cap evaluated in human factors validation study in use scenario 1: Administration of Drug, task 1.

2. Footnote 6 states that this guidance does not apply to ANDAs but that an applicant with an ANDA may find a URRA useful, especially in conjunction with comparative analyses, therefore it will apply to ANDAs. Propose to include ANDAs within the scope and add 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)*" to the list of guidance on page 2.
3. Most of the examples contained within the draft guidance seem to have been written with injectable products in mind. While we appreciate that the list of examples is not intended to be exhaustive, certain common products such as orally inhaled and nasal drug products (OINDPs) may raise distinct considerations that would benefit from a specific example, particularly in the context of an existing product that would be subject to the amendment process. Please therefore include more examples for OINDPs throughout the text and in the Example Table on that last page of the draft guidance.
4. The draft guidance states that in 'certain cases', the draft guidance may also apply to stand-alone prescription drug products that are the subject of an IND, NDA or BLA and to stand-alone non-prescription drug products that are the subject of an IND or NDA (lines 25-32) but does not elaborate on the scope of such cases. In Case Study D (lines 357-369), the draft guidance does include an example of a drug product with a complicated dose escalation phase however, it is unclear under which circumstances FDA would expect a URRA to be conducted beyond this specific case. In addition, it is unclear if an HF validation study may be required and a Sponsor wishes to submit a HF protocol / justification for FDA review, whether this falls under the current PDUFA VII goals for URRA submissions for Combination Products under an IND.
5. It would be preferable for FDA to align terminology across guidance documents whenever possible. For example:
    - FDA uses the term 'comparative analyses' throughout the draft guidance whereas the term 'threshold analysis was used in September 2018 draft FDA guidance "Contents of a Complete Submission of Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications".
    - It would be preferable where possible to align terminology used throughout the draft guidance with that contained within existing, commonly used ISO standards e.g. ISO 14971:2019. For example, terms such as 'use-error', 'risk' and 'hazard' are used interchangeably within the draft guidance but are distinct within ISO 14971:2019.
    - Some of the terminology used within Section C (lines 172-181) is unclear as to the difference, if any, between 'clinical harm', 'harm', and 'clinical impact'.
6. Some examples should be added for regarding user training, which could be used to minimize use errors. For example, see Critical Error Frequency and the Impact of Training with Inhalers Commonly used for Maintenance Treatment in Chronic Obstructive Pulmonary Disease - PMC (nih.gov) (2020)

7. The guidance should add considerations and examples for the integration of connected ("smart") devices and apps, which can prevent certain types of users' mistakes. See, for example:
    a) Electronic monitoring with a digital smart spacer to support personalized inhaler use education in patients with asthma: The randomized controlled OUTERSPACE trial - ScienceDirect (2023)
    b) Effectiveness, usability and acceptability of a smart inhaler programme in patients with asthma: protocol of the multicentre, pragmatic, open-label, cluster randomised controlled ACCEPTANCE trial - PMC (nih.gov) (2022)
    c) Advancing Digital Solutions to Overcome Longstanding Barriers in Asthma and COPD Management - PMC (nih.gov) (2023)

Specific Comments

Location	Original Language	Proposed Change	Justification of Proposed Change
Line 25-32	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	Recommend limiting the application of this guidance to stand-alone drug and biological products that have complex dosing or an increased risk profile.	The guidance states that 'in certain cases' the guidance may apply to stand-alone drug and biological products. However, the guidance does not clarify these' certain cases' where the guidance doesn't apply to stand-alone drug and biological products. We acknowledge that drug products with complicated dosing may need additional assessments to mitigate medication errors. However, for stand-alone drug and biologic products that do not have complicated dosing (e.g., titration, multiple vials) or an increased risk profile (e.g., emergency use) we do not believe a URRA comparative assessment is necessary to justify the omission of an HF validation study. These products have a long history of use by HCPs, caregivers, and patients in clinical or home use environments and inclusion of these products lead to unnecessary human factors studies or URRA assessment for the Agency to review. Therefore, we recommend clarifying that this guidance applies to drug/biologic-led combination products and stand-alone drug and biologic products where there is complex dosing or an increased risk profile.
Lines 39, 42-56	FDA recommends that sponsors refer to other relevant guidance documents related to product design and HF, including the following:…	ADD: - Content of Human Factors Information in Medical Device Marketing Submissions, Guidance for Industry and Food and Drug Administration Staff, December 2022 - Design Considerations for Devices Intended for Home Use, Final Guidance for Industry and FDA Staff, November 2014. - Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development, February 2016	Having all relevant guidance documents listed here would be helpful, to avoid uncertainty whether these other guidances apply

Location	Original Language	Proposed Change	Justification of Proposed Change
Lines 101-106	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, for example, as the product design changes, or as new risks are identified during development or post marketing.	Start a new paragraph. <u>For combination products, a</u> 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, for example, as the product design changes, or as new risks are identified during development or post marketing.	The preceding statements apply generally to drug-only and combination products. This paragraph is specific to combination products and associated guidances. If desired to make this more generic, we suggest to reference to the guidance relevant to drug-only product for when to develop risk assessments: **Safety Considerations for Product Design to Minimize Medication Errors**
Lines 108-126	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.	Align to content of Section IV.A of FDA Guidance "Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications"	The items that should be included in a URRA as described in the draft guidance do not align with existing guidance as to the content of a URRA submission (Section IV.A of September 2018 draft FDA Guidance "Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications")

Location	Original Language	Proposed Change	Justification of Proposed Change
Line 112	"The potential ***use errors*** and harms that may occur with those tasks"	"The ~~potential~~ foreseeable ***use errors, hazards, clinical*** harms, and severity of error consequences that may occur with those tasks"	The draft guidance explains that a 'URRA is important to help identify use-related hazards associated with the user interface design of the combination product'. However, having to identify *all* potential use errors may distract the URRA's focus from ensuring that foreseeable or likely use errors are mitigated. As stated in the draft guidance, use errors should be based on foreseeable circumstances rather than potential (line 151-152). We suggest using the term "foreseeable" throughout the draft guidance because this term aligns with the language used in ISO 14971. We also suggest adding terms that align with the headings in the example provided in the appendix. Otherwise, it may not be clear if the FDA expects only a mention of harms or if more detail is required.
Line 116	"Risk controls employed in the user interface design to mitigate the use errors"	Please include the definition of "user interface"	This draft guidance emphasizes the evaluation the 'user interface design' including associated risk controls. However, the guidance does not include the definition "user interface" which could lead to confusion regarding what is considered in scope. We recommend including the definition of "user interface" included in the guidance "Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications" (line 683).
Line 134	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.	Please cross-reference the guidances mentioned on Page 2 : • *Application of Human Factors Engineering Principles for Combination Products: Questions and Answers (September 2023)* • *Safety Considerations for Product Design to Minimize Medication Errors (April 2016)*	For completeness

Location	Original Language	Proposed Change	Justification of Proposed Change
Line 142	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.	Provide examples	Although the guidance references the knowledge tasks, the table example in the appendix does not provide an example. An example would provide clarification that knowledge tasks are described in the URRA and how they will be evaluated.
Lines 144-145	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.	Revise and clarify terminology to indicate that physical, perception and cognition tasks are all to be considered in the URRA	In the draft guidance, the term 'knowledge tasks' is introduced to describe 'tasks involving the assessment of information provided in the labelling'. This term in a Human Factors context is used to describe those tasks that cannot be assessed during simulated use (i.e.: knowledge-based assessment questions). Moreover, the term 'user tasks' in this draft guidance and other guidance documents is used with a broader meaning (i.e.: not only for physical tasks). It would be helpful if the terminology could be revised and aligned to indicate that physical, perception and cognition tasks are all to be considered in the URRA. With the intention to align more with the perception cognition action (PCA) method, it would also be helpful if the Agency could provide further guidance on the definition of 'knowledge task' so as not be confused with 'labeling specific warnings' which are not captured as a separate task but rather risk controls for use errors on user tasks.
Line 151	Reasonably foreseeable misuse.	Please define and clarify "reasonably foreseeable misuse" and "abnormal use", provide examples.	It would be good to have a definition of 'reasonably foreseeable misuse' in the guidance and align this definition with ISO 14971. Clarification required - Is it expected that abnormal use is also in scope of an URRA?

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Lines 152-153	Reasonably foreseeable misuse (including product use by unintended but foreseeable users) should be evaluated to the extent possible	CHANGE TO: Reasonably foreseeable misuse (including device use by unintended but foreseeable users, , *e.g.*, pediatric use of a product approved only for adult use) should be evaluated to the extent possible, and the labelling should include specific warnings describing that use and the potential consequences. Abnormal use is generally not controllable through application of HFE/UE processes.	This guidance includes 'product use by unintended but foreseeable users' as a reasonably foreseeable misuse. It would be helpful to have additional clarification as to what is considered 'unintended but foreseeable' and to align with the 2016 final guidance on Applying Human Factors and Usability Engineering to Medical Devices Section 6.1, which states 'Reasonably foreseeable misuse (including device use by unintended but foreseeable users) should be evaluated to the extent possible, and the labelling should include specific warnings describing that use and the potential consequences. Abnormal use is generally not controllable through application of HFE/UE processes.'
Lines 158-160	"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."	Potential use errors can also be identified from a sponsor's experience with use of the proposed product (e.g., during clinical trials or usability studies), literature review, adverse event reports, or product safety.	Previous usability studies are a source for identifying potential use errors and therefore should be included in the list.
Line 172 and Appendix URRA Table – Example Format	Identify the Potential Harms.	Please align terminology throughout the guidance.	Recommend amending title of Section III.C, text on Line 172 and Appendix URRA table to have consistent wording Clarification required - Is the expectation to have the potential harms, clinical impact, and severity? This also impacts the format of the URRA table in Appendix as it differs slightly compared to what is recommended in the Table 2 of the Draft Guidance Content of Human Factors Information in Medical Device Marketing Submissions, December 2022.

Location	Original Language	Proposed Change	Justification of Proposed Change
Line 185	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.	Add a note: "Refer to FDA Guidance Applying-Human-Factors-and-Usability-Engineering-to-Medical-Devices---Guidance-for-Industry-and-Food-and-Drug-Administration-Staff.pdf (fda.gov) for the definition of critical use errors for medical devices."	Although this guidance states it is to be used for combination products, the FDA should possibly consider that they also suggested this can be used for medical devices. It would be good to clarify that the definition of critical use errors is different for medical devices and combination products. The medical devices definition of critical task in CDRH 2016 final HF guidance is *"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."* whereas the combination products definition mentions *"would or could cause harm"* as described in "Original Language" column.
Lines 223-230	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.	Remove	The section this is part of is URRA development, and this covers through post-marketing and only references combination product associated guidance. Discussion of the risk management framework and updating the URRA is already discussed with appropriate references to both drug-only and combination products in Section II Line 98-106.
Line 225	The draft guidance states "The sponsor should update the URRA…", however it is unclear if this update will take place	The sponsor should update the URRA in all phases of the product lifecycle as part of the risk management process (change underlined) …	Added suggested text to clarify where the URRA update will take place as part of sponsor's risk management effort.

Location	Original Language	Proposed Change	Justification of Proposed Change
Lines 243-246	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.	Please include a comparison of intended user characteristics to justify equivalence.	User characteristics are important to include for comparisons.

Lines 251-254	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	For the justification, the sponsor should consider multiple factors, including but not limited to:
		• intended users
		  ○ user characteristics
		  ○ user familiarity and experience with product presentation
		• intended uses
		  ○ dosing considerations
		  ○ treatment urgency
		• intended use environment
		  ○ drug and device characteristics
		clinical impact of use errors
			This statement has a lot of repetition and overlapping categories of considerations. We suggest to rearrange / modify the content into a bulleted list as shown to more clearly group related concepts.

Line 276	-	Include example for inhalers	Only examples for pre-filled syringes and autoinjectors are available, please include inhalers and nasal products, as the approaches may differ

Location	Original Language	Proposed Change	Justification of Proposed Change
Lines 301-304	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	Please include a discussion of differences in the workflow between test and reference products. Suggest that formative studies could be used to demonstrate that labeling and packaging support safe and effective use.	For completeness
Appendix. URRA Table – Example Format **Line 396**	Footnote 1: "Some risk controls, such as low cap removal force may be evaluated by means other than human factors studies"	Please explain or give examples of "other means"	Suggest citing non-exhaustive examples of what "other means" refers to