



International Pharmaceutical Aerosol Consortium on Regulation and Science

1500 K Street NW • Washington DC • 20005
Telephone +1 202 230 5607 • Fax +1 202 842 8465
Email info@ipacrs.org • Web www.ipacrs.org

IPAC-RS Comments on the Draft FDA Guidance for Industry and FDA Staff

“Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development” (“Draft HF CP Guidance”)

(Docket Number FDA–2015–D–4848) (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf>)

These comments have been prepared by the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS), which is an association of pharmaceutical companies that develop, manufacture and market orally inhaled and nasal drug products (OINDPs). IPAC-RS seeks to advance the science of OINDPs by collecting and analysing data, conducting joint research and development projects, and engaging with the wider regulatory and scientific community on areas of importance to the stakeholders interested in the high quality, safety, efficacy and availability of OINDPs.

Given the significance of the industry feedback, IPAC-RS would welcome the opportunity to discuss these comments in an in-person meeting with the Agency or in a public workshop.

General Remarks

IPAC-RS welcomes the finalization of the CDRH Human Factors (HF) Guidance¹ and the issuance of additional two draft Guidances from CDRH² and from CDER, CDRH, CBER and OCP³ (referred to here as “draft HF CP Guidance”, which is the focus of these IPAC-RS comments). These Guidances are a positive step forward in clarifying FDA’s expectations regarding the role of human factors (“HF”) testing in combination product development. It is, however, the view of IPAC –RS that the draft HF CP Guidance³ could be further improved if it followed the approaches, terminology and definitions of the final CDRH Guidance¹ more consistently and provided references to the relevant sections of the final CDRH Guidance¹.

IPAC-RS welcomes the fact that the approach described in the draft HF CP Guidance³ aligns with the final CDRH Guidance¹ and would like to see more alignment on the details of those approaches, as explained further in these comments.

¹ FDA. CDRH. Applying Human Factors and Usability Engineering to Medical Devices. Final Guidance. 2016. <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf>

² FDA. CDRH. List of Highest Priority Devices for Human Factors Review. Draft Guidance. 2016. <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM484097.pdf>

³ FDA. CDER, CDRH, CBER and OCP. Human factors studies and related clinical study considerations in combination product design and development. Draft Guidance. 2016. <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf>

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IPAC-RS understands and agrees that the three Guidances aim to ensure that medical devices and combination products are safe and effective for the intended users, uses, and use environments. IPAC-RS shares the goal of ensuring that the device-user interface has been designed such that use errors that might occur during device use, which may cause harm or degrade medical treatment, are either eliminated or reduced to the full extent possible.

In particular, the draft 2016 Guidance "*Human factors studies and related clinical study considerations in combination product design and development*" describes approaches for identification and management of use related risks in combination products (including those associated with medication errors) throughout a product's lifecycle, from initial assessment through post-approval changes. This draft HF CP Guidance aligns with risk-based approach of overall product development (ICH Q8, Q9, Q10), and of the other CDRH Guidances^{1,2} and moves away from prescriptive requirements and checklists. IPAC-RS would welcome a more consistent application of a risk-based approach to human factors, which is in line with the risk management principles applied throughout the lifecycle of a device development, including the justification of an HF plan.

IPAC-RS commends the Agency for providing information in the draft HF CP Guidance on such important topics as:

- Human factors simulated-use validation studies;
- Device user interface labeling; use-related instructional materials and device labeling (instructions for use, training materials);
- Definitions of intended user groups;
- Knowledge tasks;
- Potential use errors that could be used as input to sponsors risk assessment (Appendix A).

The draft HF CP Guidance could be enhanced in the following areas:

- The distinction between clinical studies and HF testing;
- Clarification of the planning of HF validation studies;
- The distinction between testing done for labeling vs specific to user-interface labeling.

IPAC-RS offers the following comments, in three major areas, enumerated below:

- A. Scope and title of the Guidance.
- B. Definitions – their clarity and consistency within the draft HF CP Guidance and across other Guidances.
- C. Risk-based approaches – their consistent application to all aspects of device development and HF.

A table of minor editorial comments is appended at the end of this document.

A. Scope and Title of the Guidance

Based on the scope and intent of the Guidance, IPAC-RS proposes the following as a more appropriate title reflective of its content:

Human factors considerations in combination product design and development.

The above-proposed title would be an improvement on the current draft Guidance's title as it avoids the use of the word "clinical". This point is one of the major areas that needs to be clarified and addressed in the final version of the Guidance. Human Factors assessments are **not** clinical studies. The only common feature between the HF and clinical studies is that both involve a product (e.g., inhaler) and human subjects; (see Table 1).

In addition, the proposed title moves away from the word "study" because of the implication to clinical study. Instead, when referring to HF, the term "testing" (which suggests empirical findings) or a broader term "assessment" (which includes non-empirical justifications) should be used throughout the Guidance.

Table 1. Human Factors Testing is NOT Clinical Trials.

Human Factors Testing	Clinical Trials
Qualitative.	Quantitative.
Based on observation.	Based on measurements.
Goal is to see what the user is doing to the device.	Goal is to measure what effect product has in a patient's body.
Focus on the user's fingers manipulating the device .	Focus on patient's lungs (for inhalers), or blood levels – depending on the drug.
Never has a pre-defined end-point.	Always have a pre-defined end-point.

Clinical studies are designed to understand **what a drug-device product does to the body**. By contrast, Human Factors (HF) testing is designed to understand **what a patient does to the drug-device product**. For example, for inhalers, a clinical study would focus on the **lungs**; while HF testing would focus on the way a patient handles the inhaler. Accordingly, a clinical study always has a clinical end-point. By contrast, an HF assessment never includes a clinical end point.

The difference in goals between HF testing and clinical studies leads to important differences in approaches for design, end-points, methods of data collection, and data analysis. The Guidance should make this distinction explicitly. A failure to do so might result in confused study designs that inappropriately conflate multiple end points. This would prevent proper investigation and understanding of Human Factors, as well as potentially hampering appropriate identification and mitigation of HF-specific risks.

Some clinical studies may provide input related to HF assessment, e.g., a patient's comment about a taste of the medicine or about the handling of a device. Such feedback, however, does not turn a clinical study into an HF assessment – although it could provide input for a (separate) HF assessment.

B. Definitions and Consistent Use of Terms

The Guidance would benefit from a glossary with clear definitions and a consistent application of definitions within this Guidance, as well as across FDA Guidances. In particular, the new draft HF CP Guidance should align with the definitions in section 3 of the final Guidance “*Applying Human Factors and Usability Engineering to Medical Devices*”¹, definitions that have been in use for some time and are well understood by those involved in HF testing across industry and regulatory agencies. The definitions proposed below are based on the final CDRH Guidance and other well established and widely recognized standards.

Critical Task

IPAC-RS proposes the following definition of **Critical Task**, which is in line with the final Guidance “*Applying Human Factors and Usability Engineering to Medical Devices*”¹:

Critical Task: *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.*”

Note 1: “Harm” includes compromised medical care, as stated in the final CDRH Guidance¹. The draft HF CP Guidance should use the definition of “Harm” as given in the final CDRH Guidance¹ and use the term more consistently in place of “risk” and “hazard”, as appropriate for a given context.

Note 2: IPAC-RS suggests a consistent definition of the term “critical” when applied to tasks, use errors and use-related risks. In the context of medical device human factors engineering (HFE), the term “critical” should ***only*** be used when it means “with potential for serious harm to the patient or user”.

Under this definition, a critical use-related risk would be a use-related risk involving the potential for serious harm. Similarly, a Critical Use Error would be a use error with the potential consequence of serious harm.

This consistency would reinforce the risk-based approach, with emphasis on potential for serious harm to users, that is fundamental to medical device human factors engineering (HFE).

Note 3. Not all harm is serious. The criticality of a use-related risk should be identified in a risk assessment of a particular product. Criticality of a use-related risk is defined by the seriousness of the potential harm and not by the probability/likelihood of exposure to the harm.

Note 4. To illustrate a risk-based relationship between Critical Tasks and Critical Use Errors, consider the following hypothetical example of a failure of a Critical Task that does ***not*** include the potential for serious harm and, therefore, does not rise to the level of a Critical Use Error.

Consider the first-time use of a lever-actuated DPI for an asthma maintenance product, in which the participant holds the DPI mouthpiece downward, so that the powder from that first dose falls out on the floor. The

participant observes the powder, detects the error, self-corrects the error, and actuates the device properly multiple times thereafter.

Correct actuation of the DPI is a Critical Task but, because the failure occurred only once and the user self-corrects thereafter, there is no serious harm to the patient. In this case, the failure to accomplish a Critical Task should not be evaluated as a Critical Use Error.

Note 5. A Critical Task must have at least one Critical Use Error associated with it. In addition it may be associated with non-critical use errors.

For example, dose administration is a Critical Task if there are critical medication errors associated with the product but this does not imply that all medication errors are critical, which will depend on the therapeutic profile of the specific drug (e.g., maintenance therapy such as an inhaled corticosteroid (ICS) vs. a rescue medication such as a short-acting beta agonist (SABA)). Therefore, not all errors on the dose administration task are critical.

Note 6. Use-related risk assessment, which is conducted at the start of the device development program, would produce a list of Critical Use Errors for a given combination product. Subsequently, the Critical Tasks associated with these Critical Use Errors are included in an HF assessment.

Note 7. The new but undefined term “*serious use error*” (lines 132-133 of the draft HF CP Guidance) should be changed to Critical Use Error.

The following revision of lines 188-189 of the draft HF CP Guidance is therefore proposed (additions underlined): “Some examples of potentially critical tasks (depending on the product) to illustrate this concept include”.

Note 8. Based on the concerns and definitions explained above, the term “task failure” should be replaced throughout the draft HF CP Guidance with “use error” or “potential use error”, as appropriate in a given context.

Final Finished Combination Product

(Used in lines 107, 141, 326, 336, 357, 594, 613.)

The current definition of this new term in the draft HF CP Guidance does not match its use in the same Guidance and could thereby cause confusion. Therefore, IPAC-RS recommends revising the definition in lines 141-145 as follows (additions are underlined):

Proposed revised definition:

“***Final Finished Combination Product:*** The **final** finished combination product is the proposed to-be-marketed product ~~intended for market and~~ submitted in the marketing application. This term applies to the combined final device, drug, and/or biological product configuration including all product user interfaces (e.g., proposed packaging, ~~labels and labeling~~, instructional content from Patient Information Leaflet (PIL) [or Package Insert], such as instructions for use (IFU), including and training programs).”

Note 1. When an HF validation study is conducted, it is a proposed to-be-marketed version of the product that is being tested, not the “final”.

Note 2. The terms “labels and labeling” include a broad range of materials and information, only some portions of which are related to human factors. In the context of this draft Guidance, the focus is on HF assessments and validation, whereas some parts of labels and labeling would be assessed through other studies required by FDA (e.g., readability, comprehension), which do not involve assessment of a subject’s handling of the device.

Note 3. Moreover, the final product packaging, labels and labeling typically will not be available for the Human Factors validation study required for inclusion in the regulatory application because:

- Phase III clinical data, which are necessary for finalizing the labeling, may not be available before the start of an HF Validation study;
- The trade name typically present on the label may not be approved by the Agency prior to commencement of the HF validation study;
- The Agency may propose changes to the labels/labeling upon review of the application.

User Interface Labeling – vs – Labeling

The term “user interface labels and labeling” is used in lines 554 and 570, but is not specifically defined in the draft HF CP Guidance. There are other instances in the draft Guidance where the use of such a specific term would be helpful and more appropriate than a broader term “labels and labeling”. IPAC-RS recommends adding clear definitions, as follows.

Proposed definition of “***User Interface Labeling***”: ***instructions for use (IFU) and the instructional portions of the Patient Information Leaflet (PIL) [or Package Insert] and carton information.***

Note 1. Other aspects of product labeling such as medication guide, or medication content, are not instructional from the perspective of user-device interaction and as such should not be considered part of the user interface and should not be part of HF testing.

Note 2. Knowledge Task studies to be undertaken during HF testing should focus on the User Interface Labeling as defined above.

Note 3. Under section E starting on line 403 of the draft HF CP Guidance, IPAC-RS is supportive of the inclusion of Knowledge Tasks in lines 418, 421, 424, and 429. However, the items in lines 426-428 and 431-433 (incl. footnote 21 related to label comprehension studies), which apply to other aspects of product labeling, are NOT part of HF testing, and should be deleted from the draft HF CP Guidance. . Other Guidances exist for labeling review and comprehension (e.g., those referenced in lines 646-653).

Note 4. Based on the definitions and concerns explained above, the words “*Medication Guide*” should be deleted from line 677.

Clinical Study

The term “**Major Clinical Study (or Major Clinical Trial)**” (defined in lines 147-153, and used throughout the draft HF CP Guidance) – is a new term introduced in this Guidance. IPAC-RS requests that it be replaced with a recognized international term “**Pivotal Clinical Study**” (whose definition matches that given in lines 147-153).

Simulated-Use – vs – Actual-Use HF Assessment

There is a spectrum of simulated-use scenarios (e.g., with or without active drug, in real or in simulated environment) such that binary terminology is insufficient. The examples in the draft HF CP Guidance are confusing. Rather than propose specific definitions, IPAC-RS recommends that specific types of simulated-use testing conducted for a particular product be guided by a risk-based assessment.

Note 1. The concept of “HF Actual-Use Validation study” is new, introduced in this draft HF CP Guidance, and its objectives are unclear. More clarity should be provided on the specific objectives, outcomes, and timing of HF Actual-Use testing relative to other required testing that is currently executed on drug-device combination products (e.g., clinical trials and simulated-use HF testing). It is unclear what would be gained via such an “HF Actual-Use Validation” study that is not already gathered from the clinical study, the simulated-use HF testing, and the device robustness study (which is recommended in other Guidances related to drug-device combination products^{4,5}).

Note 2. Actual-Use Validation studies should not be a default requirement. Such studies may be justified, in rare circumstances, based on the risk assessment for a given product. Current examples given in the draft HF CP Guidance (e.g., coughing on inhalation – see lines 364-365) relate to situations that would be detected in clinical trials; it is therefore unclear why an HF Actual-Use Validation study would be necessary. It would be helpful if the HF CP Guidance provided different examples or description of the circumstances that would necessitate an HF Actual-Use Validation study.

Note 3. Based on the concerns explained above, lines 361-367 of the draft HF CP Guidances should be deleted.

HF Validation Study

(as defined in lines 131-139)

In light of the definitions and explanations set forth above, the following revised definition is proposed (lines 131-139, additions are underlined):

“*HF Validation Study*: A study conducted to demonstrate that the final finished combination product user interface can be used by intended users without **serious critical** use errors ~~or problems~~, for the product’s intended uses and under the expected use conditions. The study

⁴ FDA. CDER. Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate. 2013. <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm367643.pdf>

⁵ FDA. CDER, CBER, CDRH. Draft Guidance for Industry. Rheumatoid Arthritis: Developing Drug Products for Treatment. 2013. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM354468.pdf>

should demonstrate that use-related ~~hazards~~ risks for the ~~final~~ finished combination product (see glossary item A.2 below) have been eliminated or that the ~~mitigation for~~ residual risks **are is** acceptable; i.e., the benefit of product use outweigh the residual risk of the product. The study participants are representative of the intended users and the study conditions are representative of expected use conditions.”

Note 1. Based on existing definitions, *risks* can be mitigated or minimized, while a *hazard* always exists as a (hypothetical) possibility.

C. Consistent Application of Risk-Based Approach to HF Activities

IPAC-RS agrees with the principles outlined in sections C (starting on line 528), and section V (starting on line 580) and specifically, that sufficient understanding of the user interface should be in place to ensure the safety of the product going into a pivotal clinical study. However, prior to a pivotal clinical study, the product labeling and device design may not be final. Furthermore, since a validation study is not intended to demonstrate anything new but simply to confirm previous findings in the formative development program (consistent with Agency’s position articulated in lines 306-312 of the draft HF CP Guidance), IPAC-RS holds that it is unnecessary in all cases to have fully executed HF protocols before a pivotal clinical study. Rather, at the conclusion of the formative studies, sponsors should conduct a risk analysis, to determine whether HF validation testing is needed.

The following revision is therefore proposed (starting on line 530 of the draft HF CP Guidance; additions are underlined):

“The combination product’s specific use-related risk analysis generally informs the Agency’s expectations for whether HF information on a combination product should be submitted in an investigational application. The risk analysis itself should be submitted in the investigational application for the combination product. If the applicant determines from the risk analysis that a HF validation study is not needed, the applicant should provide the use-related risk analysis along with the justification for this conclusion. If the use-related risk analysis indicates that a HF validation study is necessary, FDA encourages applicants to submit the following HF information for feedback before commencing the HF Validation study.”

IPAC-RS commends the Agency for applying a risk-based approach, which aligns with the continuous approach to risk management that should be followed throughout the lifecycle of a combination product. In the draft HF CP Guidance, the risk-based approach needs to be applied more consistently.

For example, a risk-based approach should be followed for the analysis of residual risk, which is mentioned in the draft HF CP Guidance in the context of HF Validation studies (lines 136-139) and training (lines 265-290). The process for assessing and managing residual risks should be based on the overall risk management plan and development strategy for a particular product; and risk mitigation should not be limited to training. For illustration of possible ways to assess and manage residual risks, other Guidances (e.g., section 8.1.7 in the final CDRH Guidance¹) and FDA-recognized standards (e.g., ISO 62366, ISO 14791) could be referenced as examples, while recognizing that these are not mandatory and individual companies may also have other specific approaches.

Similarly, when discussing “*Considerations for Submission of Combination Product Human Factors Study Data*” (lines 440-444), the criteria (1) and (2) stated in the draft HF CP Guidance³ should not be prescribed as a default (since that would not be risk-based); criterion (2) should reference the draft CDRH Guidance “*List of Highest Priority Devices for Human factors Review*”²; and the entire sentence should be supplemented with the following points to consider:

- a. Are there critical tasks during which use error could result in serious harm?
- b. Is the device constituent part already used in the same patient population?
- c. Is the device constituent part already used in the same environment?

For example, in the case of Metered-Dose Inhalers (MDIs), the answers for the above criteria would be a) No, (b) Yes, and (c) Yes. Therefore, MDIs may not necessarily require additional human factors studies, subject to the user task analysis confirmation.

Minor Editorial Comments

Location	Original Text	Proposed Change	Rationale for Change
Table of Contents	<i>"B...1...2...C....D...."</i>	Correct headings and page numbers. Indent subsection titles "1, 2," etc	Headings and page numbers on the Table of Contents between pages 9 and 14 do not match with the document. Add indentations for clarity
Line 106	<i>"For purposes..."</i>	"For the purposes..."	Missing word.
Line 75-80	<i>"... design validation must include a risk analysis... As part of the risk analysis..... informs the device design development"</i>	Revise for a more logical flow.	Currently information appears not to be in the most logical order. Risk Analysis informs the device design development and then design is validated.
Line 153	<i>"...extension study. ."</i>	Remove second full stop.	Typo.
Line 179, footnote 18	<i>"...see Sections 7.3 and 7.4 of Applying Human Factors and Usability Engineering to Optimize Medical Device Design at http://www.fda.gov/RegulatoryInformation/Guidances/ucm259748.htm"</i>	Correct the reference.	Sections number listed should probably be 6.3 and 6.4 (not 7.3 and 7.4). Also, the link gives error "Page Not Found".
Line 195	<i>"...this task could result in needle sticks"</i>	".this task could result in needle stick injury ."	Missing word.
Line 203-4	<i>"The user being able to distinguish a product from others of similar appearance. Failure to successfully perform this task could result in delivery of wrong drug."</i>	"The user being able to distinguish a product under development from others already on the market of similar appearance being used in the same environment or by the same user group ."	The revisions are clarifying, since comparison is only possible to products already on the market. Also, as there are numerous products already on the market of potentially similar appearance, the analysis should be restricted to those products

Location	Original Text	Proposed Change	Rationale for Change
		Failure to successfully perform this task could result in delivery of wrong drug.”	that are likely to be in the same environment or used by the same user groups.
Page 7, footnote 18	“...see Sections 7.3 and 7.4”	“.... See Sections 6.3 and 6.4”	Incorrect reference.
Line 369, III.D.2	“The other type of HF Actual-Use Validation study in a real environment of use.”	“The other type of HF Actual-Use Validation study is in a real environment of use.”	Missing word.
Line 505	”Validation study assessments”	Delete “assessment” or revise the sentence starting on line 504, to read “... should be assessed through new HF Validation studies ”.	The word ‘assessment’ is confusing because not used nor defined in the Guidance previously. As such, this word could be read to mean that the need for a study should be assessed, which is probably not what the Agency intended, but it’s unclear as currently written.
Line 545	“The draft HF Validation study protocol;...”	Add a footnote reference to <u>Sections 1-7 of Appendix A in the FDA Guidance on Applying Human Factors and Usability Engineering to Medical Devices.</u>	Cross-referencing the final CDRH Guidance would strengthen the link and consistency between the Guidances, and will also provide readers with information about recommended format of the HF Validation protocol.
Line 554	“ ...labels and labeling being ”	Complete the sentence.	Currently this is an incomplete sentence.
Line 601-2	“... the data to support safety and efficacy of the combination product may adequate without... “	“... the data to support safety and efficacy of the combination product may be adequate without...”	Missing word.
Line 618	“...meetings”	“...meetings.”	Missing period.