IPAC-RS Comments on FDA Draft Guidance for Industry "Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications Guidance for Industry and FDA Staff" (Sept 2018[1])

https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621902.pdf

29-Nov-2018

IPAC-RS welcomes the publication of the FDA Draft Guidance for Industry 'Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications Guidance for Industry and FDA Staff' (Sept 2018) which provides the Agency's thinking and expectations related to Human Factors content in industry submissions, and which in turn should enable more complete submissions thereby enabling faster product reviews and, ultimately, approvals.

IPAC-RS is an association of companies that develop, manufacture or market orally inhaled and nasal drug products (OINDPs), and for some time have an established working group focused on the area of Human Factors (HF). This Human Factors Working Group, composed of subject matter experts from difference companies across the consortium, allows a collective assessment of the latest industry challenges and thought processes related to Usability Engineering and associated Human Factors development, in an attempt to ensure a consistent, considered, risk-based approach to the application of excellence in OINDP-related device development programs. A list of current IPAC-RS members and further information are available at http://ipacrs.org.

IPAC-RS has provided detailed comments to the Agency on previous Human Factors-related Draft Guidances. For example, see https://www.regulations.gov/document?D=FDA-2016-D-4412-0003; https://www.regulations.gov/document?D=FDA-2015-D-4848-0004; https://www.regulations.gov/document?D=FDA-2011-D-0469-0023 and https://www.regulations.gov/document?D=FDA-2017-N-0086-0005. Most of these Guidances have not yet been finalized, nor has there been an opportunity for a detailed public discussion or engagement with the Agency

[1] FDA Docket page: https://www.regulations.gov/docket?D=FDA-2018-D-3275 and Federal Register Notice: https://www.federalregister.gov/documents/2018/10/01/2018-21243/contents-of-a-complete-submission-for-threshold-analyses-and-human-factors-submissions-to-drug-and

on the many comments provided. In the IPAC-RS review of this latest Draft Guidance, it seems that industry's concerns have either not been addressed or have yet to be fully reviewed and considered by the Agency. For example, a significant area of feedback on the most recent HF-associated Draft Guidance, "*Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*" (January 2017), was specifically related to the approach to Comparative-Use Human Factors Studies. While there has been no public comment from FDA on the industry feedback provided to the Docket, nor an opportunity to engage in a meaningful thorough discussion with FDA in a public forum, it appears from this latest Draft Guidance (Sept 2018) that the approach to this study type has not changed from FDA's January 2017 Draft Guidance, despite significant concerns raised by the industry (both IPAC-RS and others).

A constructive dialogue is critically important. IPAC-RS appreciates, therefore, the opportunity to reiterate key points and to provide further comments in response to this new Draft Guidance. First section below presents comments of the overarching nature. This is followed by specific line-by-line comments (where the **most critical comments are highlighted in navy bold**).

IPAC-RS welcomes FDA's increased focus on publishing guidances in the area of Human Factors in recent years. Given that this latest Draft Guidance is focused on the content of industry submissions to FDA, IPAC-RS strongly believes that this is an appropriate juncture for the Agency to discuss publicly all industry comments related to Human Factors approaches. IPAC-RS would welcome an opportunity for an in-depth interactive discussion with the Agency, for example in a public workshop, at the earliest opportunity.

General Comments

1. Overall, IPAC-RS welcomes this Draft Guidance as a positive step forward in clarifying the FDA expectations for Human Factors information in industry submissions.

2. This current Draft Guidance references other Draft Guidances, which is not a recommended practice as it could result in discrepancies across these guidances as they become finalized, while also requiring additional control of sequencing of the closure of these guidances. Any changes to the finalized guidances would also require updating of multiple guidances to maintain alignment. For this reason, it is recommended to combine the relevant information from this recent Draft Guidance and the other existing Draft Guidances (e.g., "*Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development*"/Feb 2016[2], "*Considerations in Demonstrating Interchangeability with a Reference Product*"/Jan2017[3], and "*Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*"/Jan2017[4]) and therefore remove the necessity for this separate Guidance. There are so many HF – related Guidances coming out of different centers at FDA, that it would seem logical to create a single umbrella guidance to ensure consistency of approaches.

3. There are significant discrepancies between this recent Draft Guidance and other existing HF-related Guidances issued by FDA (e.g., "*Applying Human Factors and Usability Engineering to Medical Devices*"/draft in 2011, final Feb2016[5]). IPAC-RS is requesting that the Agency align all these Guidances – some of which are issued by CDER or CBER, others by CDRH – because many companies develop drug-device (or biologic-device) combination products, as well as stand-alone

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[2] https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm484345.pdf

[3] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf

[4] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536959.pdf

[5] https://www.regulations.gov/docket?D=FDA-2011-D-0469

pharmaceutical or biological products and medical devices. Companies need consistency in quality management systems, and therefore regulatory approaches to Human Factors should be harmonized for all these product types, regardless of which FDA Center publishes a Guidance for Industry.

4. The concerns raised in the IPAC-RS responses to these other Guidances[6] still apply to the current Draft Guidance. For example, see key industry positions explained in the previous IPAC-RS Comments, such as:
   - The Nature of Human Factors Studies is Essentially Qualitative
   - Goal Should be Safe and Effective Use and Substitutability Rather Than Quantitatively Minimizing Differences
   - Scientific Validity of Quantitative Approach for HF Studies Not Established
   - Other Ways Exist to Ensure Appropriate Design

5. Scope of this Guidance seems to include both NDA and ANDA submissions, which is broader than the scope of previous Guidances. The scope should be aligned / harmonized across previous Guidances (e.g., including drug-device combination products but excluding all other products that do not have a device component).

6. As this Draft Guidance is currently presented, the information within Section IV appears sequential in time. For example, would a Use-Related Risk Analysis submission be required in all cases prior to a Human Factors Validation Study Protocol submission? It is also not clear what Human Factor submission type applies to which type of marketing submission. Our proposal is to identify what Human Factors submission type is required for each marketing application, and the sequence they should be submitted in, if applicable. Alternatively, as proposed previously in this response, the relevant information from this Draft Guidance could be transferred to the previous Draft Guidances on Human Factors.

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[6] For example, see https://www.regulations.gov/document?D=FDA-2016-D-4412-0003; https://www.regulations.gov/document?D=FDA-2015-D-4848-0004; https://www.regulations.gov/document?D=FDA-2011-D-0469-0023 and https://www.regulations.gov/document?D=FDA-2017-N-0086-0005.

7. The request that to-be-tested product samples for Human Factors protocol submissions and to-be-marketed product samples for Human Factors report submission is a challenging one from a timing and logistics perspective. While it can be beneficial to provide samples, we believe this should not be a requirement but instead voluntary option for the sponsor. At a minimum, more flexibility on the condition of these samples should be allowed. The requirement for intent-to-market samples can be difficult to meet while the product development is still underway. This is specifically the case for outer or secondary packaging along with a finalized instructions for use (IFU). It is highly appreciated that the review timings have been shortened, however applicants still have to balance these expectations with development timelines. The footnote in the draft guideline is appreciated, however it may be worth mentioning acceptable alternatives, as well as an explanation/rationale for, and purpose of, the samples for the review. Further details on this topic are contained within the specific comments below.

8. It should be stated more explicitly that processes described in Section D *Threshold Analysis* and Section E *Comparative Use Human Factors Study Protocol* are for Generic products to demonstrate comparative usability with Reference Product. More clarity would be appreciated on expectations for the risk assessment process for new combinations using the same device system. Any additional HF data could be required based upon whether there is a change in the target patient population and/or user environment.

9. The Human Factors Engineering (HFE) report proposed in the CDRH guidance "*Applying Human Factors and Usability Engineering to Medical Device*s" is a good approach to integrate the Use-Related Risk Analysis, HF validation study protocol and report together. Following that Guidance also avoids redundancy of repeating some background information such as intended use. IPAC-RS recommends that the sponsor have the option of submitting one overall HFE report instead of several individual submissions of Use-Related Risk Analysis and HF validation study protocol and report. We further suggest that the Agency consider a two-step approach: 1) before the final submission, the sponsor should submit the HF validation study protocol with a partially completed HFE report (since section 8 details of the Human Factors validation testing is not done at this time); and 2) As part of the final dossier submission, the sponsor should submit the finished HFE report with the validation study protocol attached.

10. IPAC-RS suggests that the Human Factors validation study report or the Comparative Use Human Factors study results report have a standalone section to capture the deviations from the study protocol, including rationale and potential impacts for these deviations. This section does not belong in the background information and should be included in the study details section.

11. For each submission type in In (III)(A)(1), the cover letter subject line is provided in Appendix A (1). However, the leaf titles in (V)(C) are very similar to the cover letter, which seem adequate to describe a SUBMISSION, but not necessarily individual documents (e.g., formative studies, use-risk analysis, validation study). Further, the leaf titles as recommended in this Guidance for requests for review contain words like “Request” which would not be appropriate when these same documents are submitted in the marketing applications; current eCTD practice is to use the same leaf titles and “replace” them in later submissions. Can FDA clarify the leaf titles for individual documents (e.g., use-risk analysis, formative studies, validation studies, etc.), since the leaf titles listed seem more appropriate for the overall submission?

12. Footnote 21 in (IV)(B)(3) states that tasks that could lead to overdose or underdose should be categorized as critical and prioritized for testing, presumably (based on the Guidance title), Human Factors testing. Under what circumstances would a clinical study, rather than a positive Human Factors testing, be necessary? What questions should a sponsor ask in the request for Human Factors validation protocol review to identify if FDA would require that the marketing application have clinical data, rather than a positive Human Factors study? Companies in IPAC-RS have reported receiving this surprising feedback from FDA.

13. Section (IV)(A) states that a use-related risk analysis can justify that a Human Factors validation study is not needed. In order to avoid having to repeat the submission/feedback cycle in case FDA disagreed, would a sponsor be at a disadvantage if they submitted a Human Factors validation protocol for comment, while simultaneously using the use-related risk analysis to justify that a Human Factors validation study is not needed?

14. Please align throughout the document the use and spelling of the word “analysis” (singular) vs “analyses” (plural).

Specific Comments:

Location	Original Language	Proposed Change	Justification of Proposed Change
56-58	As part of evaluating drug and biologic products for safety and effectiveness, FDA will evaluate **HF data** submitted by sponsors in support of the product user interface when submission of such data is warranted	The term 'HF data' is not defined. Please provide a definition (for example all information provided by the manufacturer as described in section IV)	Without defining the term, it is not clear what is being referred to. Is the use-related risk analysis 'HF data' ? Definitions should be aligned with the other HF guidance documents already published by FDA. For device platforms that have been through the review& approval process once, sponsors should be able to justify use of a no-HF or reduced-HF protocol.
Section 3A / Line 73, section 4C / Line 210, 5/ Line 406	**"HF Validation Study Results Report" and "Human Factors Validation Study Report"**	**Human Factors Engineering (HFE) / UE Report**	**The comprehensive HF information submitted as part of a premarket submission should be called a HFE/UE Report and not a HF Validation Study report. The contents of this submission contains more information than just data from the validation study, and the title of the submission should reflect that to reduce confusion. The proposed title maintains consistency with 2016 FDA CDRH HF guidance. Additionally, line 114 of the current proposed guidance refers to this as the HFE Report, potentially signaling that the terms are being used interchangeably. Use of one consistent term will reduce confusion.**

Location	Original Language	Proposed Change	Justification of Proposed Change
Line 110 footnote 13	However, because probability is very difficult to determine for use errors...	However, because probability may be very difficult to determine for use errors...	For certain products that are commonly used and well understood, there may be more knowledge that can be used to determine probability of occurrence of harm (e.g. product complaint databases, clinical and commercial use, usability studies). Therefore, it is recommended to soften language around the difficulty of determining probabilities of occurrence of harm.
Line 110 footnote 13	Therefore, it may be appropriate when conducting the use-related risk analysis to focus on the resulting harm, and including estimated occurrence rates may not be needed.	Therefore, it may be appropriate when conducting the use-related risk analysis to focus on the resulting harm.	Critical tasks should be defined in terms of reasonable likelihood for a serious harm to occur, and including estimated occurrence rates help provide context for why a task may be defined as critical. Some tasks may have the potential to result in serious harm, however the risk of harm is remote and consideration would be impractical (e.g. death by infection as a result of not washing hands or from a cut from opening packaging).
Line 117 to 138	The risk analysis submission should include: A comprehensive and systematic evaluation of all the steps involved in using the proposed product (e.g., based on a task analysis) … …	We recommend that the order of this section be adjusted. Description of intended product users, use, etc. should come first, together with the product user interface and summary of known use problems with previous or similar products	It would be helpful if reviewers knew the intended use and user interface before they review the risk analysis. The descriptions of intended use and use interface set the stage of risk analysis. The summary of known use problems provides inputs to the risk analysis and should be presented before the details of risk analysis.

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117-138	**The risk analysis submission should include: A comprehensive and systematic evaluation of all the steps involved in using the proposed product (e.g., based on a task analysis) … …**	**Add:** • **Predefined risk acceptance criteria of the product** • **Risk assessment of each hazardous situations based on the risk acceptance criteria**	**Risk acceptance criteria and risk level assessment for each risk scenario should be included, which is a critical part of the use-related risk analysis**
121	known problems	known use problems	wording
Lines 132 - 141	"-Description of intended product users, uses, use environments, and training (if applicable) -Graphical depiction and written description of product user interface (see Appendix C for example) - Summary of known use problems with previous or similar products - Summary of preliminary analysis and evaluations, including formative evaluation"	These bullet points should be listed under a "1. Background" Heading, similar to how these elements are listed in sections 4B and 4C. The remaining bullets can be listed under a "Risk Analysis" heading.	This organizes the submission clearer, and mimics the structure of the other submissions in the guidance
138	Summary of known use problems with previous **or** similar products	Summary of known use problems with previous **and/or** similar products	Should both previous and similar products be considered? Or should similar products only be considered when no previous products exist? How is this requirement different from the requirement in line 120? IF they are addressing the same point, the two requirements should be combined in the guidance.
Page 5, line 139-140	**Summary of preliminary analyses and evaluations, including formative evaluation**	**We recommend that this summary be presented before the final risk analysis**	**This summary is the development history of use-related risk analysis given the findings of formative studies should be reflected in the final analysis**

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			already. We suggest that the development history belongs earlier in the document rather than at the end of the document.
Page 5, line 157	1. Background … …	The content of this section is in the Use-Related Risk Analysis already and the sponsor should be allowed to reference it or have the option of providing a brief summary	Please include in the Guidance the option for the sponsor to cross-reference rather than repeat.
Line 195, section 4B, footnote 21	**Tasks that could lead to harm (e.g., underdose or overdose), including those requiring the user to respond to alerts or alarms, should be categorized as critical and prioritized for testing. A task requiring comprehension of warnings, caution statements, or contraindications in the product labels or labeling would generally be considered a critical knowledge task. See Combination Products Human Factors Draft Guidance... for definition of critical tasks.**	**Tasks that, if performed incorrectly or not performed at all, would or could lead to serious harm, where harm is defined to include compromised medical care, should be categorized as critical and prioritized for testing. See Combination Products Human Factors Draft Guidance... for definition of critical tasks.**	**The definition of the term "critical task" should be made consistent with the definition in the CDRH final HF guidance. This includes defining a critical task as that which would or could cause 'serious harm' rather than harm in general. Additionally, rather than call out specific hazards (e.g. underdose or overdose) or actions (comprehension of warnings, caution statements, etc.) that should be connected with critical tasks, the product specific hazard assessment and use-related risk assessment should drive the determination if a task is critical. Distinct critical task examples already exist in the guidance document that is referenced, so the included reference to the draft FDA guidance should suffice. Additionally, the referenced guidance already indicates that risks associated with warnings,**

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			caution statements, and contraindications in the label should be included in the risk assessment.
Page 6, line 198	**Definition of successful performance or failure of each test task**	**This should be considered a deviation, not necessarily a critical failure.**	**It is hard to predict all possible use events of each test task before conducting the study. Sometimes users deviate from the instructions but still finish the task without causing unacceptable risk. We believe that this should not be considered as a failure. Use events should not only be divided into success or failure as we believe there is a spectrum, and the definition is covered in the Moderator script. We believe the sponsor should be allowed to have some flexibility when defining the spectrum.**
Line 201	subjective	objective	Validation testing script is designed to elicit facts not feelings. The interview should be about collecting objective evidence, not subjective evidence.
Line 203	Methods for root	Include text acknowledging that sometimes this may be impossible, as the level of reasonableness varies across actions by real human beings. .	The request is impossible because there can be no root cause for a subject that does the most unpredictable action.
P. 7, line 208	**Product samples (5 samples of product that will be tested in the HF validation)**		**Clarification on what needs to be included with the samples (secondary packaging, IFU, carton labeling, PI, etc.) Many of these physical items will not be**

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			ready at the time of the protocol, given the review time. We suggest the Agency consider the option of providing those samples during the study protocol review time. **Sponsors do not have relevant data during an IND**
Section 4C, line 287	**5. Product samples (5 samples of intend-to-market product)**	**5. Product samples (5 representative samples of intend-to-market product)**	**Additional guidance should be provided to provided flexibility on the representativeness of the intend-to-market product. For example, final printed labelling (i.e. US Patient Information) may not be available packed in the carton until after label negotiations are complete and language is final. In this case, substitute blank Patient Information Insert may be in the carton with labelling language submitted electronically in the submission.**
Line 210 to 285	C. Human Factors Validation Study Report	While the content for this report is similar to that within "Applying Human Factors and Usability Engineering to Medical Devices" Guidance, it does differ in terms of structure and layout. In order to keep this consistent the proposal is to keep these identical by either copying the information from Appendix A of "Applying Human Factors and Usability Engineering to Medical Devices" or referring to it.	Many companies produce both combination and medical device products under the same procedures, so by keeping the requirements across these consistent it ensures efficient and consistent generation of these reports.

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		Companies should have the option of doing it either way. An alternative approach (different from CDRH) should be acceptable.	
Line 220-228		At the end of bullet c, add language to say that sponsors should only do an additional HF validation study commensurate with the level of risk.	Can we swap bullets c and d. The logical path is to do the study, do the risk benefit and then determine if you need to do any more. Don't have to do a clean study every time.
Footnote 25	**If the HFE process identifies no use errors or problems that could result in harm**	**Please delete "no", to read :"If the HFE process identifies use errors or problems that could result in harm "**	**Typographical error that makes the sentence incorrect.**
Page 9, Line 291-292	**Threshold Analyses generally are utilized……**	**Threshold Analysis generally are utilized in comparing two drug products that contain the same medicament intended for use in the same target patient population but in a different drug delivery device……..**	**To be very clear tha these studies are targeted at generic products that are trying to establish comparability with the Reference Innovator product**
Page 9, line 294 to 297	**Labeling comparison (a side-by-side, line-by-line comparison between the proposed product and the product it references that includes the full prescribing information, instructions for use, container labels and carton labeling, and descriptions of the products)**	**Labeling comparison (a side-by-side comparison between the proposed product and the product it references that includes the full prescribing information, instructions for use, container labels and carton labeling, and descriptions of the products). The IFU comparison should be results driven and focus on whether the two instructions teach users how to**	**A line-by-line comparison of labeling is possible for the full prescribing info, but for the instructions for use (IFU) and container/carton labeling, it can be very difficult to do. In many cases, the generic and RLD are designed to have quite different cartons for the purpose of differentiation. A line-by-line comparison will be hard for the reviewers to read and understand.**

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		complete certain task and provide safety information the same way	**We believe the comparison of IFU/carton should be task and warning based. For example, do the two instructions teach users how to complete certain task differently? Do the two instructions provide the same warnings/precautions?** **Sponsors should be allowed to use a threshold analysis approach for two different drug products as part of HF, outside of substitutability.**
302-304	Physical comparison of the device constituent part(s) (e.g., **examine, through a visual or tactile examination, the physical features of the product** that it plans to reference and compare them to those of the proposed product)	Please clarify to what extent the physical features should be examined. An example showing the level of detail would be of great benefit.	
Page 9, Line 306 to 309	Sponsor's determination of whether design differences exist and, if so, whether they are characterized as minor design differences or other design differences, and the rationale for each characterization.	Sponsor's determination of whether design differences exist and, if so, whether they are characterized as minor design differences or other design differences, the rationale for each characterization and proposed acceptability of these differences.	We suggest that the sponsor assess the acceptability of the differences between the proposed product and the product it references
Line 328-330, 376-378	**Statistical Analysis…..**	**Add language from the previous IPAC-RS comments on the comparative analysis**	**Why do the Generic need this and the Innovator does not? An RLD user arm should be included to address this.**
Line 342	Subjective	Objective	The scripts are designed for facts not feelings

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Line 399-400	Sponsors should submit…	Delete	Sponsors are not providing HF studies for IND studies only at File time. This paragraph should explicitly clarify that sponsors may provide HF Validation Study Protocols for the NDA/BLA file and not in support of our INDs. The IND is a mechanism to submit a protocol for HF, but it's not (should not be) a requirement.
Section VI, lines 490 fwd	**FDA will review all threshold analyses or comparative use HF submissions consistent with good review management principles and practices, as applicable, and in a timeframe to support any applicable performance goals under FDA's various user fee programs, taking into consideration the specific circumstances (e.g. breakthrough designation) surrounding the individual application.**	**Timelines are not provided for cases where a Use Risk Analysis that identifies there is no need for a HF validation study, is submitted. The proposal is to include a timeline similar to that of the HF protocol review timeline.**	**Decisions related to the acceptability of this approach for a specific product can have a significant impact on development timelines, for example if the conclusion was that the Use Risk Analysis and other information did not support the decision that no HF validation study is required this would trigger a HF program for this product.**
Glossary, Lines 579 to 685	Text provides definitions to terms such as critical task, user interface, human factors validation testing,	Glossary is not provided in "Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development", instead it references the existing "Applying Human Factors and Usability Engineering to Medical Devices" guidance. The proposal is to follow that approach here by listing the relevant existing guidance's instead of relisting these terms here. Only terms that	In order to keep these definitions consistent across all the relevant guidance documents they should be listed in one location to prevent differences between their definition. If one guidance is updated, there will be a disconnect with the others going forward.

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		are specific to this guidance should be listed within the glossary.	Relevant information and definitions from this guidance should be added to the other draft guidances.
Glossary, line 605	**Critical task: A user task which, if performed incorrectly or not performed at all, may cause harm to the patient or user, where "harm" includes compromised medical care.**	**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.**	**The definition of the term "critical task" should be made consistent with the definition in the CDRH final HF guidance. This includes defining a critical task as that which would or could cause 'serious harm' rather than harm in general.**
Glossary, line 649	Residual use-related risks: The risks that remain after risk control measures have been taken.	Residual use-related risks: The use-related risks that remain after risk control measures have been taken.	Definition should be specific to use-related risks.
669-671	Use error: A user action, or lack of action, that was different from that expected by the manufacturer and that caused an outcome that (1) was different from the result expected by the user, (2) was not caused solely by product failure, and (3) did or could result in harm	Please consider aligning this definition of use error with the definition given in IEC_62366-1-2015 Medical devices – Part 1: Application of usability engineering to medical devices.	IEC_62366-1-2015 definition is as follows: 'USER action or lack of USER action while using the MEDICAL DEVICE that leads to a different result than that **intended** by the MANUFACTURER or expected by the USER'