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VIA ELECTRONIC SUBMISSION

August 5, 2016

Medicines & Healthcare Products Regulatory Agency
151 Buckingham Palace Road
London
SW1 9SZ
UK

Re: Human Factors and Usability Engineering – Guidance for Medical Devices Including Drug-device Combination Products

Dear Sir or Madam:

The Combination Products Coalition ("CPC")[1] welcomes the opportunity to offer comments on the Medicines & Healthcare Products Regulatory Agency's ("MHRA") draft guidance entitled "Human Factors and Usability Engineering – Guidance for Medical Devices Including Drug-device Combination Products" (the "Guidance"). We believe the Guidance promotes harmonization with other existing guidelines, such as the United States Food and Drug Administration's ("FDA") Center for Devices and Radiological Health ("CDRH") human factors ("HF") final guidance ("CDRH HF Final Guidance"),[2] the draft guidance regarding high priority devices for HF review[3] and the draft guidance regarding HF studies in combination product design and development.[4] CPC encourages further alignment on the details of those approaches, as explained further in these comments.

[1] The CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in combination product issues. One of our top priorities is to work collaboratively with regulatory agencies on issues affecting combination products to advance our common mission: providing the best possible health care to patients. Our diverse, cross-industry membership permits the CPC to bring a special, broad and unique perspective to these issues. Additional information regarding the CPC and our positions is available on our website, http://combinationproducts.com/.

[2] FDA, CDRH, Applying Human Factors and Usability Engineering to Medical Devices, Final Guidance (2016), http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdfeDocuments/ucm259760.pdf.

[3] FDA, CDRH, List of Highest Priority Devices for Human Factors Review, Draft Guidance (2016), http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM484097.pdf.

[4] FDA, CDER, CDRH, CBER & OCP, Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development, Draft Guidance (2016), http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf.

The CPC has collaborated with the International Pharmaceutical Aerosol Consortium – Regulation & Science ("IPAC-RS") in the preparation of these comments and while the sets of comments are not identical, they are very closely aligned and have many areas of similarity. This reflects the consistent view of the Guidance across the combination product industry.

Major comments are presented first, followed by detailed comments presented in a tabular format.

I. Major Comments

This part addresses multiple comments arranged into six sections: (A) scope, (B) definitions, (C) risk management, (D) Figure 2, (E) manual validation and (F) consistency with existing standards.

A. Scope

1. The statement that combination products are within the scope of the entire Guidance should be placed earlier in the document rather than at the very end. The text of the Guidance should accordingly mention not only "medical device" but "drug-device combination product" throughout, with appropriate context added with regard to risk management plans, hazards and critical tasks, which may be approached slightly differently in combination products.

   The term "drug-device combination product" should also be added to the definitions section (page 5) because it is currently not a legally recognised term in the UK or the European Union.

   Where the situation for combination products differs from that of stand-alone medical devices, it should be clarified. For example:

   - Section 6 (p. 18-19, Simulation) should recognize that the "clinical simulation" is not applicable to drug-device combination products because their clinical effectiveness is due to the drug component and is studied in clinical trials; whereas the separate HF studies are needed only to evaluate the handling of the device by the users of these combination products.

   - Section 7 (p. 20, Post-market surveillance) should acknowledge that typically, only reactive post-market surveillance is done for combination products (e.g., complaint investigation) rather than pro-active post-launch user interviews.

   - Section 9 (p. 23) should mention that for drug delivery devices with well-established platforms (e.g., pre-filled syringe based autoinjectors), the risks associated with the device components are well known, which should simplify the planning of HF studies.

   - The phrase "…expectations in different jurisdictions may vary" (p. 23) is unclear. Does it refer to jurisdictions within MHRA or outside the UK? It is not clear why this is mentioned only in Section 9 (for combination products) and not for other medical devices.

2. The target audience of the Guidance should be stated explicitly and clearly in the beginning of the document to avoid its misinterpretation or misapplication. For example, we propose adding the following sentence to the Introduction:

> *This guidance is intended for manufacturers and developers of medical devices and drug-device combination products. Physicians, NHS, NICE, and other stakeholders may find this guidance useful, but it does not apply to healthcare professionals making clinical decisions or in their practice of medicine.*

   In line with the above clarification, the sentence at the top of page 6 ("This guidance does not apply to clinical decision-making relating to the use of medical devices.") should be deleted or re-worded. If that sentence is retained, further elaboration and examples of this exclusion should be provided, otherwise it may raise questions about what types of devices fall into this excluded category.

3. It would be helpful to emphasize in the Introduction that although the Guidance aims to clarify regulatory expectations, it is not a *compliance requirement* because alternative approaches to demonstrating safe and effective use could be proposed by product sponsors.

4. Finally, the Guidance should clarify in the Introduction that it does not apply retrospectively to products already approved and marketed in the UK.

B. Definitions

The current list of definitions is incomplete and not well aligned (p. 5, 16-18 and 23). All definitions should be brought into a single section defining all terms. Furthermore, some of the provided definitions deviate from those given for the same terms in other standards and guidelines (e.g., "use error" and "abnormal use").

Therefore, we suggest that the following terms be defined – either by reference to specific guidelines, or directly (following definitions given in existing standards and guidelines):

- Drug-device combination product
- User interface (and clarify that it includes packaging)
- Risk
- Risk/benefit analysis
- Residual risk
- Hazard
- Use error
- User group (consider roles, e.g., patients, caregivers, physicians; as well as situations, e.g., disease severity and co-morbidities, demographics, care settings at home or hospital or in the field)
- Critical task
- Critical use error
- Validation study
- Summative study

Note 1: "Summative" and "validation" appear to be used interchangeably within the document. We suggest that definitions for these terms be added to the definitions section, and used consistently and appropriately.

Note 2: The Guidance introduces the term "essential task" (p. 16) in addition to using a well-established term, "critical task." The need for the new term, "essential task," is unclear since the required studies are quite correctly focused on critical tasks. The given definition (linking essential tasks to any use of a device or the frequency of an action) is also questionable. CPC suggests removing the term "essential task" from the Guidance.

NB - The term "essential task" does not appear in the FDA draft and final HF guidances or in IEC 62366. The "critical task" examples provided by FDA in its guidances cover both critical and essential tasks. Therefore, we recommend deleting "essential task" to minimize confusion.

Note 3: CPC proposes the following definition of "critical task," which is in line with the CDRH HF Final Guidance:

> *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.*

Additionally, in accordance with the above-given definition, the several different definitions of "critical task" given on page 16 (twice) and page 17 (twice) should be removed.

Note 4: The Guidance uses the term "normal use" (p. 6), but does not define it. Either this term should be avoided or MHRA should provide a clear definition that does not overlap with or contradict other established terms.

C. Risk Management Approach

1. The Guidance should strengthen the risk-management approach as a foundation to all recommendations throughout the text. The need for a particular study should be dictated by a risk assessment, rather than by default. Text should be revised accordingly throughout, especially in Section 5 (pp. 15-18).

2. The concept of "residual risk" is very important, and should be defined and discussed in the Guidance. No product ever has zero risk; however, all risks have to be identified, assessed, mitigated, managed and balanced against intended use and medical benefit, and any residual risk has to be acknowledged. This should be discussed, e.g., in the last two paragraphs on page 4, and that thinking should be reflected in the rest of the Guidance.

3. CPC suggests that in the establishment of the risk management program for a delivery system, a map of the differing use errors for a delivery system be developed against the impact to drug delivery to the patient. This would be used to develop use error classifications for the delivery system under development and enable a Usability Engineering / Human Factors program to establish upfront what errors were considered acceptable or not for the drug in question, and particularly, to define critical use errors. Defining critical use errors as part of the risk management program will enable use errors

observed in HF studies to be assessed for their impact to the patient in terms of impact on dose delivery and safety.

D. Figure 2

We believe that Figure 2 (p. 11) should be revised as there are elements of the current flow diagram which are "must-do," while others need not be mandatory or could be achieved by different means than as stated in the boxes. However, the iterative nature of the risk assessment/management and the learning-improving-testing cycle is not sufficiently clear. Some information/steps are missing. For example, risk assessment should lead to identification and then a prioritization of critical tasks. Figure 3 on page 7 of the CDRH HF Final Guidance (shown below) is much clearer and should be referenced or, if possible, reproduced in the Guidance.

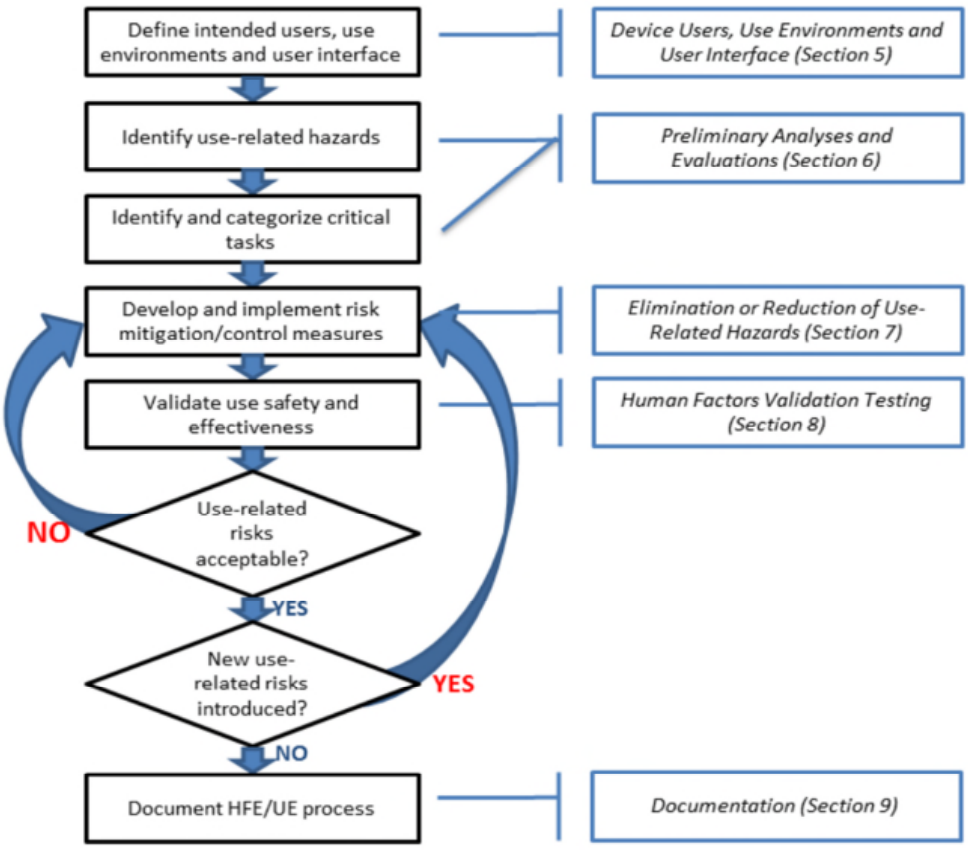

***Figure 3**: Addressing Use-Related Hazards in Risk Management* [from ref.[2]]

Examples of issues raised by the current Figure 2 in the Guidance include:

- The consideration of the human factors engineering ("HFE") process should be represented as more continual throughout the life of a product. This would also reduce the sequencing glitches (e.g., section 5.2 is not in line with 5.3; section 5.4.5 is missing).

- Risk management should be displayed as occurring throughout the product lifecycle, rather than as occurring at a single point in time. Risk management is

performed throughout the lifecycle of the product as specified in EN ISO14971:2012. Medical devices — Application of risk management to medical devices.

- Currently, the figure contains an unclear feedback loop from "Summary HF Report" to "Formative Testing and Design Iteration" and potentially to the "Risk assessment of use and use error" blocks via a "New User Error Identified" block. Identification of use error likely would not occur while generating the report, but rather during the prior step ("Summative testing/design validation"), and even that would be more of an exception than the rule. Identification of a new use error would typically occur within formative testing or summative testing, and those occurrences should feed back into the risk assessment and continue through the process loop from there. Also, arrows are missing around "New use error identified."

- Section 5.4.2 details "HF validation," but it is not clear from the diagram how this differs from Summative testing in section 5.4.4. We suggest removing "HF validation" from 5.4.2.

- The box labeled "Prioritize tasks and user interface characteristics related to safety" implies (incorrectly) that only tasks and user interface characteristics related to safety are considered in developing design requirements and formative testing. All tasks and user interface characteristics should be considered in the following steps. The wording could be revised as follows: "Prioritize all tasks and user interface characteristics with those related to safety receiving top priority."

- We recommend eliminating the "Design fixed" step from the figure, as this is a milestone and not an activity. If including milestones in the Guidance is desirable, one approach to including milestones could align with IS013485:2016 required design review points.

E. Manual Validation

1. In section 5.4.4.1 (p. 17), the final sentence ("The manual validation should be completed before commencement of the overall summative study on the device.") should be removed or revised. Manual validation can reasonably be conducted in parallel with, or as part of, the validation study, if appropriate formative-type studies have been conducted in its development.

2. In general, the requirement should be that *all aspects of the user interface* (including a manual, or instructions for use) have been tested and found adequate/acceptable. The relative timing/sequencing of the testing of different aspects of the interface, including whether to combine tests of several elements in a same study or to have separate studies testing specific elements, should be for the sponsor to decide and justify.

F. Consistency with Existing Standards

References to relevant ISO or FDA guidelines should be made more consistent in the Guidance. MHRA should either reference all such documents, or explain why one is referenced, but not the other. It would also help if the Guidance stated explicitly that

approaches as per the referenced guidelines and standards are acceptable to MHRA albeit not necessarily required if an alternative approach is justified by a sponsor.

Additional editorial comments related to referenced standards include the following:

1. The draft FDA guidance from 2011 referenced below Figure 1 has now been replaced with the CDRH HF Final Guidance dated 2016.
2. References to 62366 are inconsistent throughout the document, i.e., "EN" and "IEC" are used (e.g., see p. 8) Also, EN 62366:2015 Part 1 (e.g., mentioned on p. 5) is not yet published as the official European Norm (EN).[5] Please explain whether the 2008 version is acceptable or provide the specific EC Official Journal reference.
3. Formats "EN xxx" and "EN ISO xxx" are used (e.g., p. 9). Please use one only.
4. Standard EN 9080 (Symbols for use) has been superseded by EN 15223 (p. 9).

II. Detailed Comments

The comments presented in the table below aim to provide more detail related to the major comments presented in Part 1. There are also additional minor comments included within the table.

Section	Page	Item/ Paragraph	Comments/Proposed Replacement Text
1	3	Human Factors, Ergonomics and Usability Engineering: Why They Matter for Patient Safety	Revise first sentence in paragraph to read: "The terms 'human factors,' **'usability' and** 'ergonomics' may be considered interchangeable…" The section conflates three terms, but does not make it clear how the three terms should be treated. It first mentions that Human Factors and Ergonomics can be interchanged. Later in the section, it introduces Usability engineering or Human Factors implying interchangeability of Usability as well, but is not explicit.
1	4	Figure 1	The outcomes section of this diagram appears to be ranked from "Safe & Effective" to "Unsafe" and then "Ineffective." Suggest reordering with unsafe at the bottom as not all ineffective devices are unsafe.
1	5	Defining the Terms	In this section, and throughout the document, it is not clear if the user interface includes packaging. Suggest clarifying that in this section.
1	5	Defining the Terms	The document incorporates the concept of normal use within the definition of a use error and further attempts to frame these concepts in the scope of the guidance. Propose creating a separate definition of use error that is aligned with BS EN 62366-1:2015 and creating a separate definition for normal use.
1	5	Defining the Terms	The document uses a definition of abnormal risk which departs from BS EN 62366-1:2015. Also, it is not clear how any act or

[5] EC, https://ec.europa.eu/growth/single-market/european-standards/harmonised-standards/medical-devices/index_en.htm.

Section	Page	Item/ Paragraph	Comments/Proposed Replacement Text
			omission of an act could be totally beyond the control of the manufacturer. If the current definition of abnormal use is to be retained within the final guidance, then it should be revised to read: "an act or omission of an act by the operator or user of a medical device as a result of conduct which is beyond any **reasonable** means of risk control by the manufacturer and therefore beyond the scope of this guidance."
2	6	Regulatory Framework	The section, as well as other portions of the Guidance, provides a recital of usability relevant paragraphs of EC Directives, including the Medical Device Directive 93/42/EEC with amendment 2007/47/EC. Pending revisions to the Medical Device Directives (notably the MDD) may change and invalidate recited content in the immediate term. Recommend removing recital of directive content from the Guidance and replacing with references.
2	6	Regulatory Framework	The regulatory basis for why HFE is required for drug-device combination products is currently not specified (requirements of MDD Article 1(3) 2nd paragraph covering applicability to drug-device combinations).
2	6	Regulatory Framework	For drug-device combination products governed by Directive 2001/83/EC (Medicinal Products Directive), the relevance of the current European Commission guidance entitled: "Guideline on the readability of the labeling and package leaflet of medicinal products for human use" (Revision 1, 12 January 2009) should be discussed with relation to the requirements of section 5.4.4 Summative testing. Instructions for use for drug-device combination products are typically contained within the package leaflet of medicinal products.
2	6	Regulatory Framework	This section should discuss the role of Usability Engineering in relation to Clinical Evaluation; the latest version of the European Commission guideline entitled: "Clinical Evaluation – A guide for manufacturers and notified bodies under directives 93/42/EEC and 90/385/EEC" (MEDDEV 2.7/1 revision 4, June 2016) makes significant reference to product usability and harmonized standard IEC62366-1:2015.
2	6	Regulatory Framework	The essential requirements (ER) in Annex I of the MDD [4] include the requirements for ergonomics. We recommend replacing "ergonomics" with "human factors (including ergonomics, usability, and user interface)" to clarify the definition, as the term "ergonomics" used in the MDD is limited in meaning.
3	8	Standards	The document mentions the approach taken in EN 62366-1:2015 Medical devices, Part 1 Application of usability engineering to medical devices Annex C as "Usability of Unknown Provenance." Clarification is requested around the circumstances in which this approach would be acceptable (e.g., legacy products, bridging product of similar design, changes to intended use)?
3	8	Standards	The link takes you to an EC webpage that does not show EN 62366-1:2015 as a harmonised standard.
4	11	Figure 2	New use errors can also be identified during summative testing (5.4.4). Also, 5.4.5 appears to be missing from the diagram.
4	11	Figure 2	Clarify what is meant by "comparable devices." Does this mean devices with the same mode of action? Devices with the same intended use?

Section	Page	Item/ Paragraph	Comments/Proposed Replacement Text
4	12	Table 1	Change to "Human factors engineering terms and techniques" as not all the items listed in the first column are techniques.
4	12	Table 1	Suggest stating that the stages identified for each methodology are suggestions, e.g., questionnaires could be used as part of formative testing and FMEAs are used at each stage.
4	12	Table 1	The Considerations for Contextual inquiry box states: "Not suited to mobile settings." Please clarify what this means.
4	13	Table 1	Table 1 contains the concept of a FMEA, but does not appear to discuss other risk analysis tools that could be used to determine "likely causes and consequences of failures, including human error." In most cases, application of more than one risk analysis tool is appropriate.
4	13	Table 1	Under the "Stages" column of the table, it is not clear why certain line items include "formative assessment" or "formative and summative assessment" in parentheses, while other line items do not. Therefore, we recommend deleting the parentheses for consistency.
4	13	Table 1	In the second column of the "Task analysis" row, revise to read: "Supports systematic thinking about user tasks and how they are achieved with the device **including associated risks**." Task analysis is typically a basis for the use error risk analysis or failure mode analysis. A naïve user reading the Guidance might not realize the relationship of the techniques or think a single technique is sufficient for risk analysis. Reference IEC 62366-1:2015 clause 5.4.
4	13	Table 1	Change the title of the "Think-aloud" row to "Think-aloud **protocol**." This is the more commonly accepted terminology for this technique.
4	13	Table 1	Revise the third column in the "Think Aloud **protocol**" row to read: "Requires access to functioning device, **prototype or a simulation.** Data focuses on the device interaction (not the broader work context). Technique may be used in controlled ('lab') environment or in the real-world context (where safe to do so)." Requiring a functioning device is not practical and is burdensome for a manufacturer. It would delay formative usability testing until later in the development cycle.
5	15 – 18	Stages of a HFE Process	The information provided in the HFE techniques table is not consistent with the sections that follow in section 5. For example: • Contextual inquiry is linked to stage 5.1 in the table, but it is discussed in section 5.3. • Task analysis is linked to stage 5.4.1 in the table, but it is discussed in section 5.3. • Heuristic analysis is linked to stage 5.4.3 in the table, but it is discussed in section 5.3 • Expert analysis is not in the table, but discussed in section 5.3. • FMEA is linked to stage 5.3 in the table, but not discussed in the sections.
5.1	15	Identification of Users	In the "user profiles" bullet, we suggest adding "anthropometric data" to the description of the users.
5.1	15	Identification	Bulleted list should include training decay or frequency of use.

Section	Page	Item/ Paragraph	Comments/Proposed Replacement Text
		of Users	This could be part of the last bullet on training or could be a separate bullet.
5.1	15	Identification of Users	Clarify what "fidelity of test set" means. Consider adding cross-reference to section 6.1.
5.3	15	Identification of Hazards	In the second sentence under 5.3, revise to: "This can be carried out by using use failure modes and effects analysis informed by methods such as task analysis, expert analyses, contextual enquiry, and heuristic analysis." Task analysis, expert analyses, contextual enquiry and heuristic analysis provide hazard and harm safety-related data that are then risk-prioritized by a use FMEA. They do not necessarily do this on their own as suggested by the current text.
5.3	15	Identification of Hazards	Suggest text in second paragraph of 5.3 is changed as follows: "~~All possible~~ **Reasonably foreseeable** use errors associated with each step or user interface characteristic should be documented."
5.3	15 - 16	Identification of Hazards	Suggest dividing this section into two subsections: 5.3.1 for risk and hazard analyses; and 5.3.2 for other preliminary analyses such as task analysis, expert analysis, context inquiry and heuristic analysis. While both are important to identify and prioritize the essential and critical tasks for evaluation, it can be confusing to discuss both in one section.
5.4.1	16	Selection of Tasks for Evaluation	Critical and Essential tasks are defined in this section and section 5.3. Suggest moving these definitions to the definitions section.
5.4.2	16	Usability Design Requirements	Suggest changing the section title from "Usability design requirements" to "Device design requirements" because "usability design requirements" can be mistaken to mean the design of usability testing.
5.4.2	16	Usability Design Requirements	The use requirements identified in the use risk assessment related to safe and effective use have the potential to change during formative testing, i.e., new use errors identified. Suggest moving this to the validation section.
5.4.2	16	Usability Design Requirements	The "Usability design requirements" section is contained within the larger heading of 5.4 ("Formative and summative evaluation"), but includes design control activities that fall outside of formative and summative testing, including development and verification testing of design requirements. Suggest moving section 5.4.2 to its own section before section 5.4. Might be combined with section 5.3 – Identification of hazards.
5.4.3	16	Formative Testing	The Guidance identifies that Formative testing should be carried out until "confidence is gained that the device is safe and effective (that is, that no use errors leading to unacceptable risk are encountered)." The criteria for determining if risk is acceptable or not is not detailed within this document. Suggest identifying how this is determined.
5.4.4	17	Summative Testing	The summative testing section does not provide guidance on the nature or extent of training that should be provided to users (i.e., commensurate with the level of training intended vs. the worst case level of training). This section also does not provide guidance on

Section	Page	Item/ Paragraph	Comments/Proposed Replacement Text
			the need for a decay period after any training is provided. The final guidance should provide more detail on MHRA expectations on training and training decay prior to summative studies.
5.4.4.1	17	Validation of the Manual or Instructions for Use	Section 5.4.4.1 identifies that the manual validation should be completed before commencement of the overall summative study on the device, though it is not clear why this should be the case. Further, the guideline in section 5.4.4.2 identifies that the validation study should "not include prompts or requests to review manual." Based on these requirements, it would mean that the validation of the manual and validation of the device would need to be done as two different studies with different users. Performing the Validation of the device first and then the manual means that the study can be combined into one. This is also more reflective of actual use as the user will first interact with the manual as they normally would, i.e., not explicitly be required to review it, and then these users can be involved in validation of the manual. The order of IFU validation and system validation should not be regulated so tightly. It is possible to adequately validate the IFU and the system in one test, especially for simple systems. Consider removing the statement noted above.
5.4.4.1	17	Validation of the Manual or Instructions for Use	Revise text in the first paragraph of 5.4.4.1 to read: "The study should be carried out in the same format as a summative test and must be on the ~~final text and layout~~ **an IFU representative of the final text and layout.**" The study should be carried out on labeling that is representative of the to-be-marketed version. Following validation, changes generally can be expected to occur to the labeling and IFU prior to submission and prior to regulatory approval, however, any changes should be unrelated to the validated critical IFU use steps. Examples of such changes may include, but are not limited to, updating information in the IFU unrelated to validated critical use steps to align with the product information as it is being finalized for submission, and changes made during regulatory review.
5.4.4.2	17	Validation of the Device/ System	This section states: "The study must…include all tasks which have identified use errors with a resulting harm (critical task)." This should be clarified as not all use errors with a resulting harm must be critical tasks, depending the on range or the scale for harm severity used. Suggest replacing with: "The study must…include all critical tasks (those which have identified use errors with a resulting harm of sufficient, predetermined severity)."
5.4.4.2	17	Validation of the Device/ System	The second sentence in 5.4.4.2 states: "This is a design validation of critical tasks..." It should also include essential tasks seeing that essential tasks are required to be performed in order to use the device. Bulleted list below should state: "Include all essential tasks."
5.4.4.2	17	Validation of the Device/ System	The first item in bulleted list ("Include all identified user groups") is not correctly bulleted.
5.4.4.2	17	Validation of the Device/	Revise second bulleted item to read: "Be carried out in a realistic simulated environment or ~~in a clinical setting~~ **in an actual**

Section	Page	Item/ Paragraph	Comments/Proposed Replacement Text
		System	**environmen**t if simulation cannot provide a realistic environment…" "Clinical setting" does not represent the home use environment if this is the intended use environment of the product.
5.4.5	18	Summative Testing Reporting	In the second sentence, change from "Patterns of use errors…" to "Use errors…" Terminology has fallen out of favour. All use errors, whether or not in a pattern, should be reviewed.
5.4.5	18	Summative Testing Reporting	Suggest first sentence is revised as follows: "Following the summative testing all use errors identified **on critical tasks** should be reviewed for root cause and assessed for residual risk."
6	18	Simulation	Suggest adopting wording from CDRH HF Final Guidance for medical devices, i.e.,: "Human factors validation testing is generally conducted under conditions of simulated use, but when necessary, human factors data can also be collected under conditions of actual use or as part of a clinical study. You should perform human factors validation testing under conditions of actual use when simulated-use test methods are inadequate to evaluate users' interactions with the device. This determination should be based on the results of your preliminary analyses."
6	18	Simulation	It would be beneficial to include examples of the types of simulations that are considered acceptable for various types of medical devices.
6	18	Simulation	Suggest removing aerospace example – not relevant since such sophisticated programs and equipment rarely exist for medical devices.
6.1	19	Fidelity	Recommend revising first sentence under "Full-mission simulation" to: "Full-mission simulators replicate the **full use** environment ~~of clinical care~~." This is because not all use environments are in a clinical care setting (e.g., at-home use or emergency field use). Recommend similar revision with respect to the first sentence under "Location," i.e., "High fidelity simulation emulates all the characteristics of a healthcare environment." This should be similarly reworded to include any potential use environment of the medical device.
6.1	19	Fidelity	This section could also include the use of surrogates such as medical manikins, injection pads, surgical simulators, or other devices used to help simulate a medical procedure.
6.1	19	Fidelity	This section discusses the need for high fidelity clinical simulators as part of the usability testing environment. This is costly and not required for a large number of products – in particular drug-device combination products. We suggest adding a third section under 6.1, which would read: "3. Low fidelity simulated use environment Usability testing can be conducted in lab based environments that simulated the important and relevant aspects of the actual use environment including ambient light, noise and workspace

Section	Page	Item/ Paragraph	Comments/Proposed Replacement Text
			limitations without a full-mission simulator."
6.3	19	Moderation/ Facilitation	The "Choice of participants" section can still talk about choosing participants that belong to the appropriate user group. The section indicates that studies for some devices, such as surgical tools, have to be simulated. But the "participant" is typically the user, which is not always the same person as the patient. There still needs to be a discussion around selecting participants that accurately represent the intended users in order to create a high-fidelity simulation.
6.3	19	Choice of Participants	There is no detailed discussion of users to be included in usability testing. We recommend adding the following language: "Participants in usability testing should represent the range of intended end users of the device. If the device has more than one distinct population of users, then participants from each user population should be included in testing. In Validation, it is recommended that a minimum of 15 participants from each distinct population are included. Distinct populations may be defined based on the role of the user in using the device (e.g., patient, caregiver, healthcare professional), relevant personal characteristics that may be distinct within each population (e.g., experience, age, etc.) or any other meaningful differences. Manufacturers should justify the distinct user populations included in usability testing based on the intended users of the product."
6.3	19	Choice of Participants	The guidance should allow flexibility to utilize representative surrogate participants in HF studies when the manufacturer can provide a rationale for doing so. For example, with difficult to recruit patient groups (e.g., rare diseases), it may be required to represent end users with closely matched surrogates. We recommend adding the following language: "For certain distinct user populations (e.g., patients with a rare disease) it may be challenging and unrealistic to recruit a sample of these participants to participate in HF studies. Under such circumstances, surrogate participants may be recruited to represent the intended end users, provided a justification can be made on the basis of closely matched characteristics."
7	20	Post-market Surveillance	Suggest identifying the EN 62366 "Evaluation of a User Interface of Unknown Provenance" for existing products that have not followed a formal HF process.
7	20	Post-market Surveillance	MHRA is asking manufacturers to obtain data from competitors in order to examine complaint files in establishing known use problems. These types of complaint records are considered proprietary by manufacturers and are not available for analysis. This MHRA requirement will be difficult, if not impossible, to meet. Adverse event and recall data is more likely to be publically available. Suggest revising sentence toward the end of the third paragraph in section 7 to state: "This review should include complaints data for potential use error for their own and **(when available)** similar products and comparable competitor products. **Publically available adverse event and product recall data should also be reviewed**."

Section	Page	Item/ Paragraph	Comments/Proposed Replacement Text
7	20	Post-market Surveillance	This section should address how Periodic Safety Update Reports (PSUR) should be considered as in the EU post-marketing Safety Reporting for drug-device combination products are covered under Periodic Safety Update Reports.
8	21	Product Life-cycle	Suggest identifying the EN 62366 "Evaluation of a User Interface of Unknown Provenance" for existing products that have not followed a formal HF process.
8	21	Product Life-cycle	The second sentence of section 8 refers to "combination products." To be consistent, this should instead refer to "drug/device combination products."
8	22	Figure 3	We request further explanation regarding the purpose of this figure.
8	22	Figure 3	The positioning of the bullet points surrounding the pie-chart graphic does not seem to reflect the title of the pie pieces. For example, "Formative testing and design iteration" listed below the green piece refers to Human Factors considerations (red piece).
9	23	Combination Products	It would be helpful to have more guidance on MHRA's expectations for the type of HF information that should be provided in an MAA for a drug/device combination product with a drug primary mode of action; this includes expectations for any subsequent variations. Specifically, please provide further details on what kind of HF & Usability information should be submitted and in what format it should be presented. Also, where should it be presented within the application? It is assumed it should be in 3.2.R within the eCTD format – we suggest that MHRA confirm this in the Guidance.
9	23	Combination Products	The second sentence in the second paragraph of section 9 refers to "combination products." We request clarification of terminology at the start of the document.
9	23	Combination Products	For drug-device combination products and instructions that have been validated through HF testing, we request clarification that readability testing would not be applicable for device labelling.
10	24	References	We suggest adding: EN 15223-2 Medical devices — Symbols to be used with medical device labels, labelling and information to be supplied — Part 2: Symbol development, selection and validation. This standard has 2 parts which are relevant to the use of symbols and HF.
11	26	Further Reading	AAMI HE 48 and AAMI HE-74 are obsolete. HE-75 is not a tutorial to HE-74. It is a design principles standard and not a process standard. Accordingly, we recommend the following change: '~~ANSI/AAMI HE48 (1988-2009) 'Human factors engineering guidelines and preferred~~ ~~practices for the design of medical devices'~~ ~~ANSI/AAMI HE74 (2001-2010) 'Human factors design process for medical devices'~~ ANSI/AAMI HE75 (2009-) 'Human factors engineering – Design of medical devices'~~ (a tutorial to HE-74)'~~

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We hope our comments are helpful to MHRA as it develops its final guidance. If the CPC can help in any way, please do not hesitate to contact us.

Yours faithfully,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition