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# IPAC-RS Comments on the Draft MHRA "Human Factors and Usability Engineering – Guidance for Medical Devices Including Drug-device Combination Products"

(https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/528495/MHRA_Human_factors_draft_guidance_June_2016.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 includes a range of companies that bring forth innovator and/or generic products for oral inhalation or intranasal administration.

OINDPs are drug-device combination products, in which a therapeutic formulation and a delivery system must be integrated for administration of medicine. Some of these are marketed as a single, 'integral' product (e.g., a pressurized metered dose inhaler), while others are 'non-integral' because they may have components to be assembled by the user (e.g., a nasal-spray pump to be inserted into the bottle containing formulation). As such, OINDPs are currently subject to both medicinal product and medical device regulations; therefore an overall alignment of development and regulatory approaches in those areas has an added significance for 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.

## General Remarks

IPAC-RS welcomes the Draft Guidance 'Human Factors and Usability Engineering – Guidance for Medical Devices Including Drug-device Combination Products', ('the Guidance') and the direction towards harmonization with other existing guidelines, such as the FDA CDRH Human Factors (HF) final guidance,[1] and the draft guidances from CDRH[2] and from CDER, CDRH, CBER and OCP.[3] IPAC-RS encourages further alignment on the approach to Human Factors and Usability

[1] 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

[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

Engineering during device development and lifecycle management, as explained further in these comments. Major comments are presented first in this letter (Part I) along with explanation for the comments raised, followed by a tabulation of minor editorial comments (Part II).

# Part I. Major/Critical Comments

This part addresses multiple comments arranged into six sections:

i. Scope,
ii. Definitions,
iii. Risk Management,
iv. Figure 2,
v. Manual Validation, and
vi. Consistency with Existing Standards.

## *(i). Scope*

1. Although the title of the guidance includes the term 'Drug-device combination products', considering that this terminology is not currently defined in UK regulations, IPAC-RS proposes that the narrative in section 9 'Drug delivery devices and drug-device combination products' be placed earlier in the document rather than at the end of the document. Additionally, the scope of the Guidance should clarify this intent and reflect that specific aspects of risk management plans, hazards and critical tasks may be approached slightly differently in drug-device combination products.

   The term '**drug-device combination product**' should also be added to the definitions section (page 5) because it currently is not defined or recognized outside the US.

   Given that aspects of Human Factors (HF) and Usability Engineering may be different between stand-alone medical devices and drug-device combination products, a number of clarifications are suggested:

   - Section 6 (pp. 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 thereby studied in clinical trials; whereas separate HF studies are required to evaluate the safety and effectiveness of the handling of the device by users of these combination products.

   - Section 7 (p. 20, Post-market surveillance) should acknowledge that typically, only reactive post-market surveillance is undertaken 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., pressurized metered dose inhalers), the risks associated with the device components are well known, which should simplify the HF approach. For example, a risk-based approach and usability assessment may be more appropriate for such systems based on the intended user group and environment of use, as opposed to undertaking additional HF studies.

- Section 9 should also explicitly state that for drug-device combination products, Human Factors are usually studied with placebos, unless the use of active drug is necessary to assess Human Factors (i.e., to assess users' handling of the product).

- Section 9 (p.23): The phrase '…expectations in different jurisdictions may vary' is unclear. Does it refer to jurisdictions within MHRA or outside the UK? IPAC-RS requests clarification of the purpose of this statement, as it is placed specifically in the section for drug-device combination products but not for stand-alone medical devices.

2. The target audience of the guidance should be clarified, and explicitly stated to avoid misinterpretation or misapplication. For example, IPAC-RS suggests to add the following sentence:

   *'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 them or other professionals making clinical decisions.'*

   In line with the above clarification, the sentence (at the top of p. 6) '~~*This guidance does not apply to clinical decision-making relating to the use of medical devices*~~.' should be deleted or re-worded.

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

4. Finally, the Guidance should clarify, in the Introduction, that it does not apply retrospectively to medical devices and drug-device combination products already approved for the UK market.

## *(ii). Definitions*

The current list of definitions is incomplete, narrow, and fragmented (pages 5, 16-18, 23). All definitions should be brought into a single section defining all terms to ensure consistency throughout the document. Furthermore, some of the provided definitions deviate from those given for the same terms in other standards and guidelines (e.g., 'use error', 'abnormal use'); such alignment is suggested to ensure consistency with other aspects of the Guidance, which refer to ISO and FDA guidances on the same topic(s).

Therefore, IPAC-RS requests that the MHRA Guidance include definitions of the following terms, either by reference to specific guidelines, or directly (yet following definitions given in existing standards and guidelines):

a. Drug-device combination product.
b. User interface (and provide clarity as to the situations where it may be appropriate to consider packaging components).
c. Risk.
d. Risk/benefit analysis.
e. Residual risk.
f. Hazard.
g. Use error.

h. 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).
i. Critical task.
j. Critical use error.
k. Validation study.
l. Summative study.

Note 1: 'Summative' and 'validation' appear to be used interchangeably and therefore erroneously within the document. IPAC-RS requests that these terms be added to the definitions section, and subsequently that they be used consistently throughout the document.

Note 2: The Guidance introduces the term 'essential task' (page 16), in addition to using a well-established term 'critical task'. The need for a new term 'essential task' is unclear since the required studies are focused on critical tasks, as they should. The given definition (linking essential tasks to any use of a device or the frequency of an action) is also questionable. IPAC-RS therefore recommends removing the term 'essential task' from this Guidance. Note also that the term 'essential task' does not appear in the FDA Human Factors guidances or in ISO 62366. The 'critical task' examples provided by FDA in their guidances cover both critical and essential tasks. Therefore we recommend deleting 'essential task', to minimize confusion.

Note 3. IPAC-RS proposes the following definition of 'critical task', which is in line with the final CDRH 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.'***

Additionally, in accordance with the above-given definition, please remove the several different definitions of 'critical task' given on pages 16 (twice) and 17 (twice).

Note 4. The MHRA Guidance uses the term 'normal use' (p. 6) but does not define it. IPAC-RS suggests that this term be either avoided or that a clear definition be provided, which does not overlap with, nor contradict, other established terms.

## *(iii). Risk Management Approach*

- The Guidance should strengthen the risk-management approach as a foundation to all recommendations, throughout the document. 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 (pages 15-18).

- The concept of '**residual risk**' is very important, and should be defined and discussed in the MHRA Guidance. No product ever has zero risk, however it is important that all risks are identified, assessed, mitigated, managed, balanced against intended use and medical benefit, and any residual risk 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 MHRA Guidance.

- IPAC-RS proposes that in the establishment of the risk management program for the device portion of the combination product (i.e., the drug delivery system), a map of the differing use errors be developed based on the impact of errors to the drug delivery to the patient. This map, in turn, would be used to develop use error classifications for the delivery system under development, and would enable a Usability Engineering / Human Factors program to be established upfront, to specify errors as acceptable or not for the product 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 Human Factor studies to be assessed for their impact on dose delivery and on patient safety. For example, for inhalation drug-device combination products, it would be important to consider the following aspects: 1) the patients' ability to achieve an airflow necessary to operate the device (e.g., pediatric age or severe airways obstruction), and 2) the effect of prevalent conditions in the targeted age group on patients' ability to operate the device (i.e., arthritis in the elderly).

## *(iv). Figure 2 (Section 4, page 11)*

Figure 2 (page 11) should be revised. 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 stated in the boxes. On the other hand, 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 final CDRH guidance[1] (copied below) is much clearer and should be referenced or, if possible, reproduced in the MHRA Guidance.

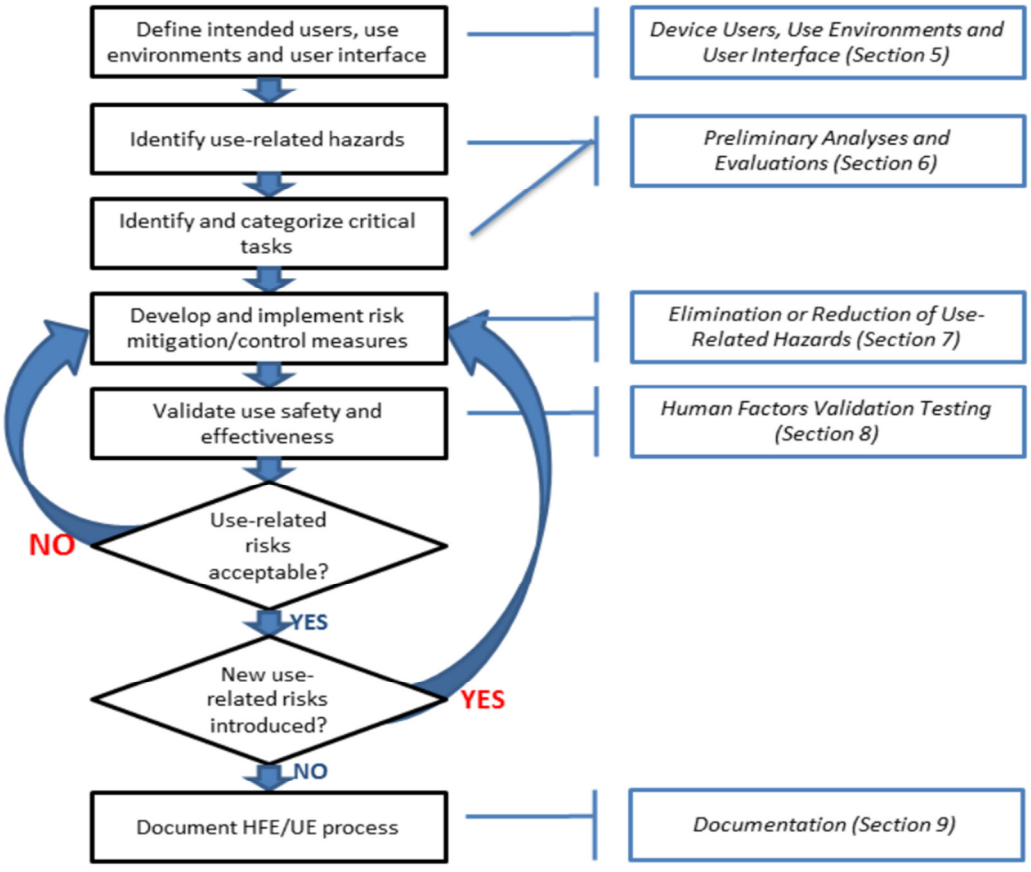


***Figure 3**: Addressing Use-Related Hazards in Risk Management* [from ref.[1]]

Examples of issues raised by the current Figure 2 (page 11) in the MHRA Guidance include:

- The consideration of the Human Factors Engineering process should be represented as continuous throughout the product lifecycle. 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 assessment should be displayed as occurring throughout the product lifecycle, rather than as occurring at a single point in time for a given program.

- Currently, the figure contains an unclear feedback loop from 'Summary human factors 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 would likely *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'.

- The box referencing Section 5.4.2 details '…and HF validation' but it is not clear from the diagram how this differs from 'Summative testing/design validation' in Section 5.4.4. Suggest removing 'HF validation' from 5.4.2.

- The box '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*.'

## *(v). Manual Validation*

- In section 5.4.4.1 (page 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. The timing and approach to manual validation in relation to usability assessments and HF studies may be different for different device-types and intended users/use environments. In the majority of cases, manual validation can therefore reasonably be conducted in parallel with, or as part of, the summative/validation study, if appropriate formative-type studies have been conducted in its development. Sponsors should state the approach in their Application, and provide suitable justification aligned with the overall HF approach to underwrite manual validation.

- 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.

## *(vi). Consistency with Existing Standards*

References to relevant ISO or FDA guidelines should be consistent throughout. Either all such documents should be referenced, or an explanation provided as to why some are referenced but not the others. It would also help if the MHRA Guidance stated explicitly that approaches per the referenced guidelines and standards are acceptable to MHRA albeit not necessarily required if an alternative approach is justified by the Applicant.

Additional editorial comments related to referenced standards:

- The draft FDA guidance from 2011 referenced below Figure 1 has now been replaced with the final guidance dated 2016.[1]
- References to ISO 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).[4] Please explain whether the 2008 version is acceptable or provide the specific EC Official Journal reference.
- Formats 'EN xxx' and 'EN ISO xxx' are used (e.g., page 9). Please chose and use one throughout.
- Standard EN 980 ('Symbols for use', referenced on page 9) has been superseded by EN 15223-1.

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

## Part II. Minor/Editorial Comments

| Section number | COMMENT | | |
|---|---|---|---|
| | *Original Text* | Proposed Change | Rationale for Change |
| Section 1 Page 4, Figure 1 | In the box 'Outcomes', the top states 'Safe and effective', while the bottom says 'Unsafe Ineffective'. | In the top part, remove 'and' to say 'Safe….Effective'<br><br>In the bottom part, switch the order to say 'Ineffective  Unsafe' | 'Safe' is not necessarily linked with 'effective'.<br><br>'Ineffective' is less injurious than 'unsafe', so should come first by the logic of the figure. |
| Section 1 Page 4, line 22 | '…assessment and mitigation of potential patient safety risks…' | Replace '~~patient~~' with '**user'** | More accurate terminology. |
| Section 1 Page 5 | '…user interface…' | Clarify whether or not includes packaging. | Evaluation of the packaging should be based on a risk assessment; and then appropriate studies should be conducted (rather than require HF studies on packaging as a default). |
| Section 1 Page 6, 2nd para | Annex I of the Medical Devices Directive 93/42/EC (MDD) [4] | Annex I of the Medical Devices Directive 93/42/**EEC** (MDD) [4] | Missing a letter. (Also the reference note should be corrected accordingly). |

| Section number | COMMENT | | |
|---|---|---|---|
| | *Original Text* | Proposed Change | Rationale for Change |
| Section 3<br>Page 8 | 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'. | Please clarify the circumstances in which this approach would be acceptable, e.g., legacy products, bridging product of similar design, changes to intended use? | This would be a valuable clarification especially for drug-device combination products, where the drug and device components may initially be developed on separate tracks. |
| Section 4<br>Page 12 | Table 1 | Add 'The stages (sections) identified for each methodology are suggestions; alternative approaches could be used if justified' | For example, questionnaires could be used as part of formative testing and FMEAs are used at each stage.<br><br>Besides FMEA, there are other risk analysis tools that might be more appropriate; and sometimes more than one tool may be used for a given product. |
| Section 5.1<br>Page 15 | 'Identification of users…' | Add to the bulleted list of considerations 'training decay' or 'frequency of use'. | |
| Section 5.1<br>Page 15 | 'user profiles…' | Add 'anthropometric data' | Some metrics beyond height (which is already mentioned) might be relevant for a given device. |
| Section 5.4.2<br>Page 16 | 'Usability design requirements' | Make its own section (not under 5.4) or add to 5.3. | Currently, this sub-section describes activities that may fall outside of the 'Formative and Summative evaluation' (which is the overall title of Section 5.4) |

| Section number | COMMENT | | |
|---|---|---|---|
| | ***Original Text*** | **Proposed Change** | **Rationale for Change** |
| **Section 5.4.2 Page 16** | 'The use requirements identified in the use risk assessment related to safe and effective use…' | Rephrase and move this bullet to the Formative studies section (5.4.3) - | The use requirements can change during formative testing, e.g., when new use errors are identified. |
| **Section 5.4.3 Page 17** | 'Use errors identified in the formative studies should be reviewed against the use risk assessment for their severity and their acceptability determined.' | Use errors identified in the formative studies should be reviewed *for* ***their potential to cause serious harm to the patient*** and their acceptability determined. | A pre-study use risk assessment may not predict all potential use errors observed during the study. Use errors should be evaluated for their potential to cause serious harm to the patient regardless of any pre-study risk identification activities. |
| **Section 5.4.3 Page 17** | 'Formative studies should be carried out until confidence is gained that the design is safe and effective (that is, that no use errors leading to unacceptable risk are encountered).' | Change to read<br>'Formative studies should be carried out until confidence is gained that ***residual risks are acceptable for the intended medical use.'*** | Safety and effectiveness does not necessarily require complete absence of risk of harm. Furthermore, mentioning 'unacceptable' risk without a detailed discussion does not add any clarity. The language therefore should be re-phrased in terms of 'residual risk' and 'risk-benefit', which are well defined and established through other existing standards. |
| **Section 5.4.4 Page 17** | 'Summative testing' | Refer readers to the FDA CDRH final guidance[1] (especially section 8.1.4 'Participant Training') for details. | Section 5.4.4 does not provide guidance on the nature or extent of training that should be provided to user, nor does it provide any guidance on the need for a decay period after any training is provided. These topics are adequately discussed in the FDA guidance.[1] |

| Section number | COMMENT | | |
|---|---|---|---|
| | ***Original Text*** | **Proposed Change** | **Rationale for Change** |
| **Section 5.4.4.2 Page 17** | 'Include all identified user groups…' | Bullet this sentence. | The sentence belongs to the bulleted list and should therefore be properly bulleted. |
| **Section 5.4.4.2 Page 17** | 'This is a design validation of **critical** tasks and information and must be carried out on a product representative of the launch product.' | Change to read ***'This is a demonstration that the product can be used by the intended users without serious use errors or problems, for the intended uses and under the expected use conditions*** and must be carried out on a product representative of the launch product.' | It is the user interface that is validated rather than specific critical tasks. |
| **Section 5.4.2 Page 17** | 'The study must…include all tasks which have identified use errors with **a resulting harm (critical task)**.' | Change to read '***The study must…include all critical tasks.'*** – if the definition of Critical Task proposed in Note 3 above is also included in the MHRA Guidance.<br><br>Alternatively, change to read '***The study must…include all critical tasks (those which have identified use errors with a potential for harm of significant, predetermined severity related to safety or efficacy***).' | Not all use errors with a resulting harm may be critical tasks.<br><br>Only those tasks that have a potential for safety or efficacy impact are critical tasks. (See also definition and discussion in Note 3 above). |

| Section number | COMMENT | | |
|---|---|---|---|
| | ***Original Text*** | **Proposed Change** | **Rationale for Change** |
| **Section 5.4.5 Page 18** | 'Those use errors resulting in an unacceptable risk will require further risk control activity/ design iteration and further usability testing to confirm that action has resolved issues.' | Replace with ***'It should be confirmed that modifications to the user interface (including the device and the labeling) would not further reduce risk, are not possible or not practicable, and the remaining residual use-related risks are outweighed by the benefits derived from use of the device.'*** | The term 'unacceptable risk' is never defined. Acceptability is a clinical assessment of risks of harm versus benefit to the patient. |
| **Sec. 5.4.6 Page 18** | '… benefit-risk status…' | Replace with '…risk-benefit analysis…' | Define, and use, terms already adopted in existing guidelines. |
| **Section 6 Page 18** | The last two paragraphs (about aerospace, pilot and nurse training) | Delete or replace with more pertinent examples | Use that space to discuss relevant aspects of medical-device and drug-device combination products' development, testing and use. |
| **Section 6 Page 19** | 'Simulation' | Consider adding examples of acceptable simulations for various types of med.devices and drug-device combination products. | |
| **Section 6.1 Page 19** | 'Full-mission simulators replicate the environment of clinical care.' | Change to '…replicate the **representative** environment ~~of clinical care~~.' | Not all use environments are in a clinical care setting (e.g., at-home use, emergency field use). |
| **Section 6.1 Page 19** | 'High fidelity simulation emulates all the characteristics of a healthcare environment'. | Change to '…emulates **relevant** ~~all the~~ characteristics of a **representative** ~~healthcare~~ environment.' | Not all use environments are in a clinical care setting (e.g., at-home use or emergency field use). |

| Section number | COMMENT | | |
|---|---|---|---|
| | *Original Text* | Proposed Change | Rationale for Change |
| Section 6.3 Page 19 | 'Choice of participants' | State that '**Participants should be representative of user groups**' and add more discussion about user groups. | Not only patients but also physicians, technicians, nurses, family caregivers are using medical devices and drug-device combination products. |
| Section 7 Page 20 | Post-market surveillance | Add more details to this discussion, especially from the perspective of drug-device combination products. | |
| Section 8 Page 21, Line 4 | 'Considering the wide range of medical devices and combination products,….' | Add to read: 'Considering the wide range of medical devices and **drug-device** combination products,…' | Add for clarity and consistency |
| Section 8 Page 21, final para | '…will occur throughout a product lifecycle…' | Add to read '…will occur throughout a product lifecycle **(i.e., post pivotal clinical studies for a drug-device combination product)'** | This would acknowledge the realities of a more complex lifecycle of a drug-device combination product, relative to that of a stand-alone medical device. |
| Section 8 Page 22 | Figure 3 | Delete the figure. | The purpose of Figure 3 is unclear, and the message is confusing. |
| Section 9 Page 23 | 'Therefore, for drug-device combination products….' | 'Therefore, for **both integral and non-integral** drug-device combination products' | To avoid misunderstanding. |
| Section 10 p. 25, ref. 18 | | Cassano-Piche, ... for Health Technology.. | Missing a letter |