EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Submission to:
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Submission of comments on 'Guideline on the quality requirements for drug-device combinations' (EMA/CHMP/QWP/BWP/259165/2019)

Draft Guideline dated 29 May 2019

At https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-quality-requirements-drug-device-combinations_en.pdf

Comments from:

Name of organisation or individual
International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS). IPAC-RS is a not-for-profit association of companies that develop, manufacture or market drug-device combination products for inhalation therapies, as well as companies that provide components or services to product manufacturers. For a complete list of member and further details, please visit https://ipacrs.org/

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	APPLICABILITY We welcome greater clarity on dossier requirements for Drug-Device Combinations (DDCs). However, as the implementation date for this draft guideline is not precisely defined, we suggest that any submission prior to or during implementation is not required to follow the final guideline. Only submissions after the referenced Regulation (EU) 2017/745 is fully applied on 26th May 2020 (assuming this draft guideline is also finalised prior to or on that date) would then be expected to follow the final guideline.	
	CRITICAL – DEFINITIONS (1) The MDR 2017/745 mentions in "Whereas" (20) that the definitions regarding devices should be aligned with well-established practice in the field at EU and at international (e.g. US FDA definitions) level in order to enhance legal certainty. We would like to raise concerns regarding the use of the wording "medical device component" by the EMA to describe the device part of a DDC, whereas the US FDA defines a "medical device component" in 21CFR820.3(c) as meaning "*any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device*", and whereas "crucial (medical device) components" and "critical suppliers of (medical device) components" are terminologies used under MDR 2017/745 with a meaning that is different from the EMA meaning ("device part of a DDC"). For the sake of having unambiguous definitions and enhance legal certainty in Europe, **we suggest that the terminology "device constituent" be used by EMA** instead of "device component".	

CRITICAL – DEFINITIONS (2)

The EMA understanding of what the device part of a DDC covers is crucial to clarify: is it covering only the piece that is indeed administering the drug (e.g. the dropper), and not the container, or is it covering the total assembly of the container with the administering piece? The consequences from an EMA and NB reviews are substantial because it impacts on the split between what the NB and the EMA intend to review, and therefore on how the manufacturers intend to organize and split their data between their MAA and the documentation subject to NBOp (NBs are supposed to review the "device part", and not the container).

IPAC-RS recognizes that there is a difficulty defining "device part" and "drug part" in various scenarios, so we would encourage EMA to establish a dialogue among all stakeholders regarding definitions and invite public comments further, perhaps outside this particular guideline's process, as a more general discussion.

DEFINITIONS (3)

DEFINITION OF TERMS INCLUDING THE WORD "CLINICAL"
The draft guideline uses the following terms in relation to the word *clinical*: investigation, trial, development, study, setting. It would be valuable to have agreement on these terms in the context of the DDC draft guideline. …

Clinical Trials – assess the safety and efficacy of the active drug(s) in the DDC (and can additionally be used to assess Usability aspects)
Clinical Studies – assess the safety and efficacy of a medical device (and can additionally be used to assess Usability aspects) but are not relevant to DDCs (??)
Usability (Human Factors) studies – assess the ability to use the medical device or DCC correctly and can be conducted in a clinical or non-clinical setting. DDCs should be used with placebo when in a non-clinical setting.
Clinical Development / Clinical Investigation / Clinical Setting – these terms do not have defined meanings.

CRITICAL – HARMONIZATION WITH OTHER STANDARDS

1. The draft guideline mentions that "*Ph.Eur. requirements and European and ICH guidance take precedence over ISO standards*." (line 171). However, flexibility should be introduced into the draft guideline relative to the use of harmonized standards published in the Official Journal of the European Union. Indeed the presumption of compliance of the device or device-constituent part of a DDC to the applicable requirements of the MDR 2017/745 Annex I (GSPR) can be established based on the list of harmonized standards (Article 8).
2. Please include reference to other relevant guidelines, for example, Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products, EMEA/CHMP/QWP/49313/2005 Corr as they also include guidance on what data to include on delivery device development.
3. Please also address the inconsistency with that existing guideline - Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products" (EMEA/CHMP/QWP/49313/2005 Corr (note this guidance was due to be revised in 2017, however this was put on hold). Anticipate that the inhalation and nasal guidance will be updated to align with this guidance and MDR.
4. Harmonize approach to (bio)compatibility by referencing ISO 10993 in lines 526-535.

Comment and Proposed Changes

The draft guideline mentions in Annex 2 **(Lines 812-815)** a review process and NBOp for platform technologies referring to the CEP system (Certificate of Suitability to the monographs of the European Pharmacopoeia). **IPAC-RS recognizes possible advantages of such a 'CEP-like' system (rather than a DMF-like system) meeting two key concerns raised by the Industry, which are focused around the potential streamlining of MAA / Variations management through one centrally evaluated and recognized uniform 'CEP-like' NBOp that could potentially support several MAAs. IPAC-RS understands through Lines 814-815 that this 'CEP-like' system could be used to provide evidence of compliance with the MDR Annex I GSPRs by one Notified Body for the same platform technology that is used across multiple drug-device combination products. However, the implementation of this 'CEP-like' system needs to be clarified in the following respects:**

- **The legal basis and mechanism for this 'CEP-like' system needs to be clarified. It is not clear if this would be possible under the existing European legal & regulatory framework for medicinal products.**

- The definition of Platform Technology (PT) is not sufficiently clear and needs to be more precise. The term is commonly applied within the domain of drug product formulation technology, including manufacturing techniques and/or stabilizing ingredients for drug formulations. The platform may then be adapted to multiple active ingredients. For example to optimize aspects of physiochemical properties of certain drugs which lead to poor pharmacokinetics. Specific examples include patented technologies for microspheres, nanotechnology, liposomes, oral disintegration and sustained release formulations and manufacturing. Within the text of section 4.2 and the definition in section 10, the term PT may be applied to either formulation or device. Possibly this is the intent, however, this should be specifically stated in the definition (i.e. one (only) or both).
- Within Annex 2 the responsibility for providing information on the PT is assigned to the 'technology owner' **(Lines 812-813)**, with a table (**"General Information")** that is (in effect) "a letter of authorisation to the MAH to use the data". However, ~~no mechanism for providing such data to an NB is defined. The LoA seems to be referring to a Drug or Device Master File-type system which does not exist in Europe. Therefore how the 'letter of authorisation' process will work in practice should be clearly explained~~ **the CEP system as it is in place in Europe for pharmacopoeial susbstances does not use a "a letter of authorisation to the MAH to use the data". Rather, the CEP certificate itself is intended to be introduced in the MAA to replace the relevant data. Therefore IPAC-RS questions the need of a "letter of authorization" if a CEP-like process is implemented for PT.**

The CEP procedure for pharmacopoeial substances is optional. Currently in EU, there are 3 possibilities to submit pharmacopoeial substances data (CEP; Active Substance Master File (ASMF); Full data in the MAA). IPAC-RS recommends that the CEP-like system for a PT is also explicitly left optional by EMA.

Comment and endorsement

IPAC-RS has also reviewed and supports the EFPIA EBE comments on this draft guideline.

Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Line 49-50		**Proposed Changed Text** *(i.e. co-packaged with the medicinal product or referenced **through brand name/registration number/CE mark** in the medicinal product information and obtained separately. **Reference to generic types or classes of devices do not fall within the scopes of this guideline – i.e. administer using a suitable syringe/catheter etc.**)*	
Page 3, lines 70-80		**Comment** The list contains examples, including a DPI (dry powder inhaler), but leaves out some other important and distinct drug-device combinations, such as pMDIs. **Proposed Change** Include pressurised metered dose inhalers, i.e., : *Dry powder inhalers **and pressurised metered dose inhalers** that are assembled with the medicinal component and ready for use with single or multiple doses but cannot be refilled when all doses are taken.*	

Line 95	**Comment** Alongside "nebulisers, vaporisers", please add "accessory" devices – such as mouthpieces and facemasks - to make it clear that they are also covered by the guidance as non-integral DDCs. **Proposed Changed Text** *Nebulisers, vapourisers, **mouthpieces**, **facemasks***
Lines 112-114	**Comment** Since Article 117 of MDR does not apply to ATMPs, manufacturers are not required to submit a declaration of conformity with the MAA or to ask for a positive Notified Body opinion of the device constituent prior to submitting the MAA. However, according to line 112, in some cases the guideline provisions apply to the device constituent of an ATMP when it is part of the container closure system. Please clarify if this means that the CTD of an ATMP DDC should include the device constituent information detailed in paragraphs 5 and 6 even if the device constituent won't even been evaluated by a NB.
Lines 118-119	**Original Text** *b) Electromechanical components of devices (including active implantable devices) and electronic add-ons to existing products.* **Comment** Integral DDC with electromechanical components are common, therefore some guidance in that area would be useful. In fact, the draft guideline mentions "software" (e.g., in lines 273, 371), which presupposes inclusion of at least some electromechanical components. **Proposed Changed Text** ~~***b) Electromechanical components of devices (including active implantable devices) and electronic add-ons to existing products.***~~

Line 131-133	**Comment** Presumption of conformity to MDR 2017/745 Annex I GSPR is supported by harmonized standards published in the Official Journal of the European Union. In addition, some guidance on establishing compliance to GSPR can be found on the EU Commission website. **Proposed Changed Text** *In addition, this guideline should be read in conjunction with all other relevant directives and regulations, the European Pharmacopeia and all relevant Commission, ICH and CHMP guidelines, Q&A documents,* ***list of harmonized standards****, and other documents as linked to or published on the EMA* ***and EU Commission's Medical Devices websites.***
Line 168	**Comment** Please clarify at which point during the MAA review that samples may be requested.
Line 170-171	**Comment – CRITICAL – NEED TO CLARIFY; PROVIDE SPECIFIC EXAMPLES** The change proposed below aims to clarify the quality requirements leading the development of the two constituents of a DDC (drug product and device). If the development of the device constituent is considered, Ph. Eur. chapter(s) or monograph(s) and ICH guidance cannot take precedence over ISO standards. **Proposed Changed Text** *Compliance* ***of the drug component*** *of a DDC with relevant Ph. Eur. chapter(s) or monograph(s) should be demonstrated. Ph.Eur. requirements and European and ICH guidance take precedence over ISO standards* ***as far as the requirements for the drug component of a DDC are concerned****.*

Line 181	**Comment** Should align with options presented in 5.4.2.a (line 409) **Proposed Changed Text** *Section 3.2.R should include relevant information related to the demonstration of compliance of the device(s) with MDR Annex 1 (the GSPRs) e.g. NBOp, NB Certificate of Conformity and/or device manufacturer's EU Declaration of Conformity* ***or Applicants confirmation***
Line 213	**Comment - CRITICAL** Harmonizing the nomenclature of DDC's device-constituent(s) basing on existing medical devices nomenclature databases would both support leveraging NBOp for platform technologies, and help device-constituents and DDC manufacturers with establishing state of the art required under MDR 2017/745 Annex I on GSPR. See also the General comment on harmonization. **Proposed Changed Text** *SmPC Section 6.5: The type of the device****-constitutent(s) and its (their) component material(s)*** *should be listed,* ***considering recognized medical device database nomenclature (CND codes, GMDN codes***
Line 260	**Comment** Please clarify: if the final control strategy is reported in section 3.2.P.2.3 manufacturing process development, is it sufficient to cross-link to this part of M3 in section 3.2.P.3 (reference is made to EMA/CHMP/QWP/245074/2015)?
Section P.2.4 starting on Line 261	**Comment** There is a redundancy of information within P.2.4 and P.7. Suggestion is to be more specific on the difference between the two sections or to combine all Container Closure System information in P.7.

Line 315-316	**Comment** Please clarify: if a sub-assembly operation for the device constituent is performed by a partner/contractor, should this third party be also listed in section 3.2.P.3.1 as manufacturers? (Compare also to Lines 322-325, allowing the reference to be included in section P.7 instead).
Lines 367-368	**Original Text** *Evidence of compliance with the relevant Ph. Eur. monographs, if applicable, and/or food contact Directives, as appropriate (such as declarations of compliance from suppliers).* **Proposed Changed Text** *Evidence of compliance with the relevant Ph. Eur. monographs, if applicable, and/or food contact Directives, **as far as packaging materials for non-solid active substances and non-solid medicinal products intended for oral and topical (except ophthalmic) administration are concerned (refer to EMEA guideline on plastic immediate packaging materials),** as appropriate (such as declarations of compliance from suppliers).*
Page 12, lines 378-379	**Original Text** *Simulated transport studies that encompass chemical (e.g. degradation) and physical (e.g. vibration) stability, where relevant.* **Comment** The original text is confusing, as degradation is what may be measured, and vibration is a process – the revised wording provides examples of things which cover chemical and physical aspects of transportation and also mentions the potential for actual transportation. **Proposed Changed Text** ***Actual transportation or** simulated transport studies that encompass chemical **(e.g. different temperatures)** and physical (e.g. vibration) ~~stability~~ **aspects to demonstrate stability during transportation**, where relevant.*

Lines 446-459	**Comment** Usability and human factors studies are not clinical studies, so the more appropriate location for this information is Module 3.2.R not in Module 5. **Proposed Changed Text** ~~*detailed information on usability and human factors studies (or justification for their absence) should be presented in Module 5, and a summary should be provided in Module 3.2.R (cross-referencing the detailed study in Module 5)*~~ ***A summary of usability and human factors studies should be presented in Module 3, while cross-referencing the detailed study provided in Module 3.2.R.***
Section 6 starting on line 463 "Non-integral DDCs."	**Comment** Please, consider the event that the manufacturer of the drug product and the manufacturer of the device are not the same and that the two components of the DDC have not been co-developed (with the exception of the data generated on the combination in order to demonstrate the quality, safety and efficacy of the drug product when administered through the referenced device). In the case the manufacturers of the DDC components are not the same, it could be difficult for the drug product manufacturer to retrieve detailed and specific info about the device (e.g. mechanical functionality of the device) because of not disclosable proprietary information. Please, consider the possibility for the drug manufacturer to cover the device requirements (apart from providing evidence of quality, safety and efficacy of the drug-device combination) with the reference to the Declaration of Conformity issued by the device manufacturer or to the NB Certificate of Conformity.

Line 502-505	**Comment** The change proposed below aims to clarify that the "clear narrative description" of the device is only required for the aspects related to the development of the combination with the drug (i.e. the description of device development itself is not required) **Proposed Changed Text** *This section should provide evidence for the suitability of the device(s) in its (their) intended use, provide a clear narrative of device and medicinal product development* ***intended as a combination****, and provide all relevant data (including justification of any new device, pharmaceutical form or excipient, etc., not previously used, where relevant).*
Line 523-525	**Comment - CRITICAL** For medicinal products intended to be used sterile, the sterility of the non-integral device should be verified (e.g. by reference to the CE certificate). In-use safety after opening should be assessed. For example, a sterile drug product to be administered via inhalation with a dedicated nebulizer cannot maintain the sterility once the container closure system is opened, both in a domestic as well as in the hospital environment. **Proposed Changed Text** *For medicinal products intended to be used sterile, the sterility of the non-integral device should be verified (e.g. by reference to the CE certificate).* ~~*Maintenance of sterility throughout use and shelf-life of the final medicinal product should also be demonstrated*~~*.*
Section 6.1.4 starting on line 550	**Comment** Include subheadings, to align with equivalent information provided in section 5.4

Line 598	**Comment** It is conceivable that device endpoints are included in the pivotal clinical trials especially for drug delivery devices. As such it is possible that not all the GSPR clauses will be met before the pivotal clinical trials start. **Proposed Changed Text** *Given the (often) critical contribution that a device makes to the safe and effective administration of a drug product, it is expected that the device be as advanced as possible in the development process ~~(i.e. meets the relevant GSPRs)~~ by the time pivotal clinical trials start*
Line 607	**Comment** Changes may require pharmaceutical performance data to be submitted as well as safety and efficacy **Proposed Changed Text** *Where changes are made to the device, data to bridge the different device designs from a* ***quality,*** *safety and efficacy perspective may be required in Modules 3 and 5.*
Section 8, starting on line 615. "Lifecycle Management"	**Comment** At present, the EU Variations Regulation and the associated variations guidelines do not cover a wide variety of possible changes and modifications that may affect the device constituent of a DDC during the lifecycle of the product (e.g. only addition/replacement/deletion of an integral or not integral device are considered, while the variations for container closure system are limited to some aspects or some pharmaceutical forms). Please consider the possibility to revise and update the Guideline on the details of the various categories of variations in order to widen the number and types of variations applicable to both integral and not integral device constituent of a DDC.

Line 702-704	**Comment - CRITICAL** Usability and Usability Engineering/Human Factors Engineering should be defined according to IEC 62366. **Proposed Changes** 1. Replace the definition of 'usability' with that from IEC 62 366: "***Characteristic of the user interface that facilitates use and thereby establishes effectiveness, efficiency and user satisfaction in the intended use environment"*** 2. Add the IEC 62366 definition for 'usability engineering or human factors engineering': ***Usability Engineering (or Human Factors Engineering): Application of knowledge about human behaviour, abilities, limitations, and other characteristics to the design of medical devices (including software), systems and tasks to achieve adequate usability."***
Line 812	**Comment** NBOP FOR PLATFORM TECHNOLOGIES: The draft guideline mentions in Annex 2 a review process and NBOp for platform technologies referring to the CEP process. This process and the role of the platform technologies owners (e.g., pharma company or device manufacturer, as the case may be) are very unclear and guidance needs to be provided. For example, it is not clear whether the technology platform holder's data are, under this process, still required to be included in CTD section 3.2.R., as this would prevent preserving confidentiality of the data. It is not clear as well whether this process authorizes the technology platform holder to take responsibility for obtaining of the NBOp for its platform technology device-constituent. **Proposed Change** Consider adding a separate cover sheet template for NBOp in the case of platform technologies without details of the MAH, marketing authorisation type, procedure number and items related specifically to combination product. At the time the holder of the platform technology requests a NBOp for the platform technology, the information related to the submission details of the combination product may not be available