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30 August 2019

Quality Working Party
Committee for Medicinal Products for Human Use
European Medicines Agency
PO Box 71010
1008 BA Amsterdam
The Netherlands

Reference: Guideline on the quality requirements for drug-device combinations (draft)
EMA/CHMP/QWP/BWP/259165/2019

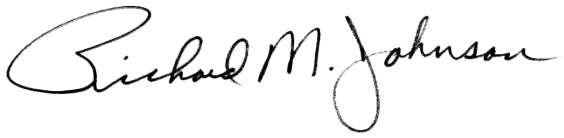
Dear Madam or Sir:

PDA appreciates the opportunity to comment on the draft guideline on the quality requirements for drug-device combinations, EMA/CHMP/QWP/BWP/259165/2019. We present our comments in the attached table.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments have been prepared by a committee of PDA members with expertise in pharmaceutical and biopharmaceutical manufacturing on behalf of PDA's Biotechnology Advisory Board and Board of Directors.

If you have any questions, please do not hesitate to contact me via email at johnson@pda.org.

Sincerely,



Richard Johnson
President and CEO

cc: Tina Morris, PDA; Ruth Miller, PDA; Falk Klar, PDA

Aug. 31, 2019

Submission of comments on 'Guideline on the quality requirements for drug-device 6 combinations' (EMA/CHMP/QWP/BWP/259165/2019)

Comments from:

Name of organisation or individual
Parenteral Drug Association

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	None	

2. 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)*
81 - 87		**Current text**: Non-integral DDCs are those DDCs for which the two or more separate components (i.e. medicinal product(s) and device(s)) are not physically integrated during manufacturing but where the medicinal product and the specific device(s) are combined for administration. Devices in non-integral DDCs are those that are co-packaged and supplied along with the medicinal product, or where the Product Information (SmPC and Package Leaflet) refers to a specific device to be used with the medicinal product but the device is obtained separately. In either case, devices not falling within the scope of Article 1(8) and 1(9) of the MDR should be CE marked. **Proposed change**: Non-integral DDCs are those DDCs for which the two or more separate components (i.e. medicinal product(s) and medical device(s)) are not physically integrated during manufacturing but where the finished medicinal product and the finished device(s) are combined for administration by the user at the time of use. Non-integral DDCs may take either of two forms. (1) The medical device is supplied to the user in the same package as the medicinal product (co-packaged), therefore forming a unique combination for the safe and effective delivery of the medicinal product. (2) The medical device and medicinal product are obtained separately, but the medicinal product information (SmPC and Package Leaflet) refers to one specific finished medical device, identified by its brand and type, that must be used to ensure the safe and effective delivery of the medicinal product. If the medicinal product information refers to a general type of medical device (i.e. infusion pump) or a specific device that may come from many manufacturers (i.e. 2 mL syringe or 29 gauge hypodermic luer needle), it is not a DDC and this guidance does not	

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		apply. In all cases, devices not integrated with the medicinal product (i.e. not falling within the scope of Article 1(8) and 1(9) of the MDR) should be CE marked. **Rationale:** PDA strongly suggests that EMA provide clearer language to help industry understand when a particular pairing rises to the level of "non-integral DDC." In many situations, a device may be recommended for use with a particular medicinal product, but with sufficient flexibility in device choice that the combination cannot be considered a DDC. In PDA's view, EMA's language in line 86 regarding "specific device to be used with the medicinal product" does not provide adequate clarity for industry to determine the combinations that are and are not non-integral DDCs. In our proposed revision, we have attempted to capture the key elements of safe and effective delivery of the medicinal product.	
98		**Comment:** PDA suggests that EMA add language to further clarify the scope of this document. We believe that the following language, which could be added at the beginning of the Scope section, matches EMA's intent. **Proposed additional text**: This guideline only addresses products where the medical device is specifically intended to administer a medicinal product, whether it is placed on the market in such a way that it forms a single integral product with the medicinal product or is provided as a separate finished medical device which is intended solely for use in the given combination with one medicinal product. It applies only to products for which the medicinal product must be submitted and approved under an MAA. This guideline does not apply to DDC where the medical devices incorporate, as an integral part, a medicinal substance or human blood derivative **with a mode of action ancillary to that of the device**.	

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118 - 119		**Comment:** PDA suggests that EMA might clarify what it intends when it refers to "Electromechanical components of devices (including active implantable devices) and electronic add-ons to existing products." As written, we believe that this language is very broad.	
142 – 153		**Comment:** PDA believes that the text in lines 142-153 could be clarified to reduce confusion. Our suggested revision follows. In addition, PDA suggests that EMA include examples of the types of devices that are addressed by each section, to aid understanding. PDA does not believe that it is entirely clear which integral devices would require involvement of a Notified Body and which would not, if they were not being used separately. In a guideline such as this, examples can be very helpful. The proposed text mentioned CE marking in line 146. We suggest omitting that reference to the CE mark because the CE mark itself is not necessary to show conformity with GSPRs. Because the CE mark is not relevant to the point being made, we suggest referring only to the Certificate of Conformity, which will help avoid confusion. The issue of CE marking on integral devices itself is a topic that could be clarified. Can integral devices be CE marked? Which types of integral devices may have a Certificate of Conformity? PDA suggests including examples or additional discussion of this topic. **Proposed change:** In accordance with Article 117 of the MDR, an MAA for an integral DDC shall include evidence of the conformity of the device part with the relevant General Safety and Performance Requirements (GSPRs). **If an EU Declaration of Conformity or Certificate of Conformity exists, that document is adequate. Otherwise the following evidence may be used**:	

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		1. For medical devices that, if used separately, would not require the involvement of a NB, the applicant's confirmation that the device part meets the relevant GSPRs. **This option would apply to devices that are Class 1 devices (not sterile or having a measuring function), including non-sterile, non-measuring, non-invasive applicators**. **2.** If the medical device, if used separately, would require the involvement of a NB **(e.g., is Class 1 sterile, Class 1 with a measuring function, Class 2a, Class 2b or Class 3)**, a Notified Body opinion (NBOp) on the conformity of the device with the relevant GSPRs, issued by an appropriately-designated NB.	
236		**Comment:** It is not clear what 'new' means. We assume that 'new' means the selected device has never been marketed anywhere in the world. **Proposed change**: … justification of ~~new~~ device ***that has not been marketed before***…	
306 - 307		**Comment**: The language 'under different orientations' is too general and may lead to unnecessary testing. PDA suggests that the 'worst-case orientation' is more appropriate. **Proposed change**: …under ~~different~~ **worst-case** orientation~~s~~…	
322		**Comment**: PDA believes that, when EMA uses the term 'DDC manufacturer' in this discussion of Integral DDCs, EMA intends to refer only to the pharmaceutical company or the CMO/CDMO that combines the drug and the device into a DDC. It does not refer to the manufacturer of the medicinal product or of the medical device, unless that manufacturer also combines the two items into an integral DDC. This understanding appears to be supported by the language in lines 328-329.	

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		Proposed change: PDA suggests that EMA consider clarifying this language, especially if PDA's interpretation is incorrect.	
345		**Comment**: 'Extractable volume' is not frequently used, and therefore may not be clear to many users. We believe that EMA means to refer to the drug volume being expelled by the device, and we recommend that EMA use those words specifically. **Proposed change**: … ~~extractable~~ volume **expelled by the device**	
431		**Comment:** It would be helpful if this guidance provided slightly more detail regarding notified body opinion (NBO) requirements. For instance, in the case of multi-component drug and device combinations, is it sufficient to combine separate NBOs from the device constituent manufacturers, or must the applicant submit an NBO for the overall combination in the drug MAA? As an example, a prefilled autoinjector may be made of purchased syringe barrels and autoinjector parts. Would an NBO be required for the syringe and autoinjector assembled as a single unit, or would separate assessments be required for each component (i.e. one opinion for the syringe, one opinion for the autoinjector)? Similarly, can a manufacturer obtain a single NBO for a platform device that is intended to be used in Integral DDCs with multiple drug products and indications, provided that the data provided to support the NBO covers the range of characteristics of multiple drug products/indications (e.g., testing with a range of viscosities, usability testing covering different patient populations concerned)?	
467		**Comment:** As described in our comments to line 81 - 87 above, PDA strongly suggests revising the phrase "specific type of administration device" to provide clarity	

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		Current text: … in exceptional cases, where the use of a specific type of administration device is specifically provided for in the Product Information of the medicinal product, additional information may need… **Proposed change**: … in exceptional cases, where the use of one specific finished medical device, identified by brand and type, is specifically provided for in the Product Information to ensure the safe and effective delivery of the medicinal product, additional information may need…	
492		**Comment:** In the description of "package leaflet and labels" for non-integral DDCs, it is currently not clear how a manufacturer would label a co-packaged device to avoid confusion. It is assumed that the outer packaging would contain reference to the DDC only to avoid confusion for the end user but this is not clear from the current text of the guidance. **Proposed change**: PDA suggests that EMA include text here similar to the text provided on lines 223-225 for integral DDCs.	
607 - 610		**Current text**: A risk assessment should be included in Module 3.2.P.2.4, which should describe the changes, batches used and trial(s) affected, and what mitigation was performed to minimise the impact on product quality. **Proposed change**: An assessment should be included in Module 3.2.P.2.4, which should describe the changes to the device, the batches used and trial(s) affected, and the mitigation or testing performed to ensure that the impact on product quality was minimal. **Comment**: The assessment provided in the Module may not technically be a risk assessment, so PDA recommends referring to it as only an assessment. Further, because testing may show that no mitigation of risks is necessary, we suggest that the assessment note either the mitigation or the testing performed.	

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621		**Comment:** It would be helpful to include more guidance about the changes that might require updates to relevant documentation for DDCs. For instance, could a change in formulation/concentration or clinical use (new indication) of the medicinal product (but without a change to the design of the device component) trigger a request for a new NBO?	
653		**Comment:** PDA suggests that EMA include the following definitions modified from the IMDRF Common Data Elements for Medical Device Identification (IMDRF/RPS WG/N19), as more clarity around the term “reusable” is highly desirable. **Proposed additional text:** ***Single Use Device:*** A medical device intended by the manufacturer to be used on an individual patient during a single procedure. ***Reusable - Single Patient Use Device:*** A medical device intended by the manufacturer to be used on a single patient, that can be refilled with additional medicinal product. ***Reusable - Multi-Patient Use Device:*** A medical device intended by the manufacturer to be used on multiple patients with reprocessing (e.g. cleaning disinfection or sterilization) between uses.	