30 August 2019

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

Comments from:

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)
	The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research and technology organizations. Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from pre-clinical, proof of concept and first-in-human studies through post-approval and pharmacovigilance research. In 2018, ACRO member companies managed or otherwise supported a majority of all biopharmaceutical-sponsored clinical investigations worldwide. With more than 130,000 employees engaged in research activities in 114 countries, the member companies of ACRO advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research. ACRO thanks the EMA for producing a helpful, detailed and comprehensive draft guideline on the quality requirements for drug-device combinations. In particular, ACRO welcomes the recognition of a risk-based approach to product development and data presentation so that alternative approaches for emerging technologies may be followed, if adequately justified. We also welcome and support the Agency's efforts to promote harmonisation of the format of Notified Body Opinions.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes
254-260		Comment: We assume that this section refers to information on manufacturing process development as it relates to the incorporation of the device with the medicinal product in order to achieve the desired characteristics for the combined product, and not to the manufacturing process development of the device *per se*. Proposed change (if any): Please clarify the above.
288		Comment: In order to avoid confusion, we recommend the following change. Proposed change (if any): Change "release until the end of shelf life" to "release until the end of the (in-use) shelf life."
376-377		Comment: The EMA has adopted ICH guideline Q1E on the evaluation of stability data for medicinal products, which allows, under certain circumstances, for extrapolation to extend the retest period or shelf life beyond the period covered by long-term data, particularly if no significant change is observed at the accelerated condition. However, the current draft guideline requires "Microbial quality, sterility, content/potency and purity for the entire shelf-life and in-use period, as appropriate", which implies that extrapolation of stability data will not be acceptable for a DDC. Proposed change (if any): State definitively whether or not extrapolation of stability data may be acceptable when establishing the shelf life or retest date for a DDC, depending upon the specific characteristics of the product.
443-444		Comment: We appreciate and support the EMA's efforts to promote harmonisation of the format of Notified Body Opinions by publishing a proposed template, and we encourage the Agency and the European Commission to take further steps to ensure the use of an agreed template by Notified Bodies designated under Regulation (EU) 2017/745. Proposed change (if any):

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524-525 And 527-528		Comment: Our comment above on lines 376-377 also applies to these statements. Proposed change (if any): State definitively whether or not extrapolation of stability data may be acceptable when establishing the shelf life or retest date for a DDC, depending upon the specific characteristics of the product.
611-614		Comment: There may be (rare) situations where a change may be made to a non-integral DDC during pivotal clinical trials, in which case the same provisions as stated in lines 601-610 on integrated DDCs would also apply. Proposed change (if any): Make clear that any change to a non-integrated DDC during pivotal clinical trials must also be described, evaluated and justified in terms of any potential impact of the changes on the quality, safety and efficacy of the medicinal product.
646-647		Comment: ACRO welcomes the recognition that flexibility is needed for emerging technologies. Proposed change (if any):
81-83 and 84-89 and 465-470		Comment: The definition of a non-integral DDC should provide a clear scope in the cases where the device is obtained separately. A medicinal product may require the usage of device(s) obtained separately to properly administer the drug solely by its nature (e.g. infusion bags, tubes, canules etc.) without these being specified in the Product Information and any product of the required devices may be used. Proposed change (if any): Please clarify if medicinal products fall into the definition of "non-integral DDC" by virtue of a general device or devices used to administer the product, or only where the Product Information makes reference to the use of a specific device product, e.g. trade name.
		ACRO thanks the Agency for the opportunity to provide feedback on this draft guideline. Please contact ACRO (knoonan@acrohealth.org) if we can answer any questions or provide additional details.