<30 August 2019>

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

Comments from:

Prescrire editorial team

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)*

1) EMA and its regulatory role in marketing authorisations for drug-device combinations:

- Many medicinal products are combined with items that fall under the status of medical devices. These drug-device combinations play a major role in preventing medication errors. When poorly designed, poorly evaluated or poorly authorised, they can cause serious adverse effects and even death. EMA's obstinacy, for example, in authorising dangerous devices, such as both versions of the *fentanyl* iontophoretic transdermal system (Ionsys°), or in not requiring that *levetiracetam* non-prefilled syringes (Keppra°) be labelled with the patient age ranges for which they are intended, is worrying.

- This public consultation relating to the new Medical Devices Regulation (EU/2017/745) is an opportunity for EMA to significantly strengthen its expertise in these health products and patient safety. EMA must safeguard its independence. Yet in its draft guideline it appears to be preparing the ground to become dependent on notified bodies (NBs) and medical device manufacturers. The recent scandals involving medical devices have shown the inability of NBs to guarantee the safety of patients who use these devices. Although Regulation EU/2017/745 appears in theory to strengthen the supervision and roles of NBs, they are likely to struggle to provide a service that increases the safety of health care if the number of NBs in the European Union falls. NBs only "verify" conformity with General Safety and Performance Requirements (GSPRs), while compliance with standards and guidelines is optional and conformity is simply presumed.

- Even if the new regulations on medical devices prove to afford a higher level of protection several years hence, the regulatory framework for medical devices, which follows the Global Approach, will never reach or approach that for medicinal products. The level of safety of medicinal products must not be dragged down by the weaknesses in regulations relating to medical devices. On the contrary, the regulatory framework for medicinal products should set the standard for the safety of medical devices.

- We urge EMA to set up its own in-house specialised committee with expertise in medical devices, similar to the CAT or COMP committees on which the CHMP relies to reach marketing authorisation decisions. Civil society expects EMA and national drug regulatory agencies to engage effectively in the safety of patients who use medical devices, especially devices for use by or on individual patients. It seems inconceivable to us that responsibility for evaluating and authorising high-risk medical devices in the European Union will not return to health authorities sooner or later. EMA has a central and major part to play in preparing for this development. The EMA Committee for Medical Devices would liaise with the Medical Device Coordination Group (MDCG).

- EMA has other aspects to address, such as organising the traceability of medical devices included in medicinal products, involving the unique device identifier (UDI) system that is due to be rolled out. How quickly and effectively will EMA respond to incidents involving such devices?
- Another issue is the matter of access to documents relating to the assessment of medical devices. The technical documentation for a medical device should be added to the marketing authorisation dossier and be accessible to any citizen through Regulation 1049/2001 on public access to administrative documents. In other words, drug regulatory agencies have a responsibility to centralise and disseminate information relating to the safety of the drug-device combinations they authorise.
- It is up to EMA to ensure that these medical devices are subject to vigilance. Currently however, there is no European medical devices vigilance process apart from the "Task Forces", and Member States' participation in these is optional. EMA should lead efforts to establish a European vigilance network for medical devices. This would be a task for the Committee for Medical Devices.
- EMA should encourage manufacturers to provide certificates confirming full compliance with European harmonised standards pertaining to the manufacture of the drug-device combinations it authorises. These certificates should be issued by independent third-party certification bodies (other than the NB involved in the CE marking process). This would be far safer than the voluntary full or partial application of standards, and self-certification of compliance with these standards by manufacturers. NBs do not verify compliance with standards with the same rigour as drug regulatory agencies verify medicinal product applications. Would EMA consider allowing marketing authorisation applicants to self-certify their medicinal products?
- As the EMA draft guideline points out, non-integral drug-device combinations (e.g. with a co-packaged medical device, such as a non-prefilled syringe provided for the oral administration of *levetiracetam* (Keppra°)), are very common and increasingly so, and integral drug-device combinations, such as the *fentanyl* iontophoretic system are likely to become more commonplace. It is likely that software and algorithms, in particular "artificial intelligence", will also become more common in the coming years. What are EMA's plans for covering the growing need for expertise in these areas? For example, how will EMA assess the first "smart" prefilled insulin pen? Will its EPAR include detailed information about the harm-benefit evaluation of the medical device part, i.e. the software and its algorithm? The obvious home for such expertise would be within EMA's Committee for Medical Devices. We also have concerns about the quality of conformity assessments, user testing, and evaluations of the risk of errors and usability, given that there is no template showing the information that is expected and therefore no guarantee that the appropriate information will be provided.
- The EMA Committee for Medical Devices would also need to monitor "drug look-alike" medical devices. There are increasing numbers of such poorly packaged products in the self-medication sector, especially from online retailers, which deceive consumers into thinking they are medicinal products. Who has the legitimacy to ban them if not drug regulatory authorities? For now, only national authorities have taken action against such products, albeit rarely, by referring them to the European Commission, one example being Commission Implementing Decision (EU) 2017/1445 that *cranberry*-containing products do not qualify for medical device status for which the opinion of the CHMP was requested.

- We urge EMA to make sure that the requirements for variation procedures are as stringent as those for initial marketing authorisation applications, especially as far as the prevention of medication errors is concerned.
- Finally, we would like to ask whether this guideline was developed in conjunction with the HMA, i.e. all the national drug regulatory agencies.

2) Dosing devices:

The purpose of most medical devices in drug-device combinations is to prepare and/or administer doses of the medicinal product. Our recommendations on such devices are as follows:

- Although this consultation concerns the quality part of the marketing authorisation dossier, EMA is right to propose firm links between quality modules and clinical evaluation modules in this area. In our view, separating expertise in quality from that in clinical safety and efficacy could endanger patients.
- Favour unit-dose packaging, to prevent the risks associated with the use of dosing devices.
- Refuse any marketing authorisation or variation application if the dosing device is not provided. It is insufficient to refer to a specific dosing device in the summary of product characteristics (SmPC) that patients should obtain separately from a health professional or company, or might buy on the internet.
- Oral liquid preparations must not be measured using household spoons or droppers.
- Refuse on principle mass-produced (non-integral) dosing devices that are not labelled or embossed with information specific to the medicinal product they accompany.
- Take other potential sources of danger into account: conversion from mg to mL; two different graduation scales on the same dosing device; potential confusion between dosing devices from the same range; etc.
- Present EMA’s evaluation of these risks clearly and in detail in EPARs.
- EMA must systematically require marketing authorisation applicants to have user tests carried out by target patient groups or health professionals. This applies not only to injectable and oral liquid drugs, but also to oral solid forms with unusual, complex packaging (e.g. oral chemotherapy drugs).
- These recommendations are mainly aimed at protecting children, elderly patients, and patients undergoing high-risk hospital care. When marketing authorisations are extended to include paediatric populations, we regularly find that the means to treat them have not been

adequately addressed: suitable dose strengths have not been marketed and a dosing device for accurate preparation of small doses has not been included in the box.

We urge EMA to take account of national and international guidelines concerning the quality and safety of dosing devices.

We would also like to take this opportunity to ask EMA to add packaging mock-ups to EPARs, as it was recommended to do by the European Pharmacovigilance Risk Assessment Committee (PRAC).

3) We have also commented on several passages of the draft guideline.

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Health Products Regulation

On behalf of Prescrire

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)*
97		Comment: all dispensing processes should be covered, in particular those used for automated dose dispensing, rather than just devices with electronic parts.	
99-107		Comment: the weakness of the regulatory framework for medical devices must in no way lower the standards EMA imposes on medicinal products.	
145-147		Comment: a better option for ensuring that manufacturers comply with European harmonised standards, which would presume conformity with the General Safety and Performance Requirements (GSPRs) for medical devices, would be for an independent third-party certification body (other than one with the role of notified body (NB)) to certify compliance with these standards. It is surprising that EMA considers self-certification by manufacturers compatible with the standards to be met by medicinal products.	
155-157 162-163		EMA must develop independent expertise in medical devices so that it can evaluate and, if necessary, qualify NB opinions on conformity with the GSPRs and usability.	
159 "or is referred to in the SmPC"		Comment: EMA must not accept this situation. Any medicinal product that must be measured and/or administered should accompanied by an appropriate, sufficiently accurate dosing device that has been assessed for quality and clinical safety and efficacy, and has undergone user testing by a target	

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		patient group and/or health professionals.	
178-182		The following information should be provided: dose per graduation unit; the standard deviation of measured values; unit of measurement of the graduation scale (mg or mL); minimum and maximum values; numbered and unnumbered increments on the graduation scale. The marketing authorisation applicant should explain and justify these choices. They should be validated by the drug regulatory agency concerned. Their evaluation should be documented in a "Usability and Packaging" section of the EPAR.	
195-198		Information about a device that formed part of a previously approved drug-device combination does not guarantee its quality and safety when combined with a different drug. The idea that technical equivalence, within the meaning of the regulations on medical devices, is transposable from one medicinal product to another could lead to unsafe drug-device combinations.	
203-204		Rather than speculating about emerging technologies, it seems far more urgent to form and operate a European committee for medical devices vigilance, similar to the European pharmacovigilance network.	
216-219 "consistent with the SmPC"		Package leaflets should certainly be consistent with, but not less informative than, the SmPC. Yet this is often the case, especially with regard to adverse effects and warnings. Package leaflets should not be "simple". They must be sufficiently detailed and must then undergo readability testing by patients and/or professionals.	
220-221		SmPCs and package leaflets should describe devices in detail	

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"symbols or pictograms" 229-230		and give detailed instructions for use, with the aid of photos and/or illustrations. Package leaflets should include a diagram showing all the components of the package, with explanations indicated with arrows, and comments.	
274-275		We expect EMA to conduct a pro/con comparison of mg versus mL graduation scales, to determine which is better for preventing medication errors.	
290		In order to prevent such issues, EMA must require marketing authorisation or variation applicants to conduct user testing by target patient groups or health professionals, including tests to determine the risk of usage errors.	
318-320 "packaging operations" + 378-379		Although beyond the aims of this draft guideline, drug regulatory agencies also need to address the issue of the stability of medicinal products when not protected by their primary packaging, in particular for the purposes of automated dose dispensing.	
331-333		Avoid markings/graduations printed on a label. Embossed markings/graduations are preferable.	
499-510		Applicants should avoid, or justify through proactive risk assessments, choosing a non-integral, and therefore mass-produced, dosing device unrelated to the medicinal product. EMA must refuse all marketing authorisation or variation applications when a dosing device is needed but not provided.	
519-520		Dosing devices must be fit for purpose and accurate. They should have no superfluous markings/graduations. They should be marked with the medicinal product's trade name and International Nonproprietary Name and, where	

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		necessary, its strength or the age range of the patients for which it is intended (e.g. *levetiracetam*).	
565-570		These studies are important: EMA would do well to draw inspiration from the FDA and Health Canada guidelines. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-product-design-minimize-medication-errors-guidance-industry The reports of these studies must be documented in EPARs.	
615-627		The medical device manufacturer must notify the marketing authorisation holder of the medicinal product of all changes. The marketing authorisation holder should take due account of the change in accordance with the rules governing variations to the marketing authorisation for its medicinal product. This is important because medical device manufacturers are not in a position to determine which changes must be reported. It is already difficult for them to identify substantial changes requiring recertification for CE marking purposes.	
628-642		Will all changes to dosing devices be subject to the requirements for type II variations? A detailed statement on the analysis of the risks arising from the change to the device should be included in the EPAR.	
649 "scientific advice"		Discussions between EMA and marketing authorisation applicants or holders to obtain scientific advice can generate conflicts of interest. The fact that the detailed minutes of these discussions are not made public fuels doubts over EMA's independence from the health products industry.	

Please add more rows if needed.