30 August 2019

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

Comments from:

Name of organisation or individual
EFA – European Federation of Allergy and Airways Diseases Patients' Associations Submitted by EFA Policy Officer Panagiotis Chaslaridis (Panagiotis.chaslaridis@efanet.org) in coordination with EFA members and the International Primary Care Respiratory Group (IPCRG) www.efanet.org

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)*
	EFA welcomes the EMA initiative to the streamlining of quality requirements for DDCs, a type of products that has seen a rise in the number of applications for commercialisation, and are therefore becoming more and more used. DDCs are of great importance for the patient community EFA represents, given that allergy, asthma and COPD are chronic non-communicable diseases that need long-term medication. Treatments for allergy and airways diseases require adherence to be effective, which is linked to the regularity and correct dosing of the medicine intake. Therefore, EFA appreciates the increasing availability of DDCs, as their automated features fit well with the long-term needs of allergy, asthma and COPD disease management. As the paper correctly points out, DDCs have the potential to relieve patients from part of the disease burden. Besides this, certain DDCs are also vital in life-threatening situations e.g. adrenaline auto-injectors in the case of anaphylactic reaction. Finally, the alignment of quality requirements has the potential to stimulate further research into better and more efficient DDCs for the benefit of patients.	

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)*
70-80, 90-97		Comment: EFA proposes that the list of examples also highlights **nasal sprays (integral), epicutaneous patches (integral) and Portable Oxygen Concentrators (non-integral)**, the use of which is expanding, among others thanks to information made available by national patient associations. Proposed change (if any): For lines 70-80 (integral) ▪ Devices for delivery to site of action e.g. the dropper on the top of the container with eye drops or the mouthpiece on the top of spray cans for throat sprays, **nasal sprays** ▪ Single dose pre-filled syringes, pens and injectors ▪ Multi-dose pens and injectors containing a pre-filled cartridge where the cartridge cannot be replaced, and the pen is not designed for subsequent use with a new cartridge ▪ Drug-releasing intra-uterine devices; pre-assembled, non-reusable applicators for vaginal tablets ▪ Dry powder 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 ▪ Implants containing medicinal products whose primary purpose is to release the medicinal product ▪ Medicinal products with an embedded sensor ▪ **Epicutaneous patches** For lines 90-97 (non-integral):	

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		▪ Oral administration devices (e.g. cups, spoons, syringes) ▪ Injection needles and filter needles ▪ Refillable pens and injectors (e.g. using cartridges) ▪ Reusable dry powder inhalers; spacers for inhalation sprays ▪ Nebulisers, vaporisers ▪ Pumps for medicinal product delivery ▪ Electronic tablet dispensers ▪ **Portable Oxygen Concentrators**	
155-157		Comment: The Competent Authority should evaluate the device-specific aspects of safety and performance that are **both relevant and irrelevant to the quality, safety and efficacy of the medicinal product**, as in some cases there is the issue of safety and performance of the device independently of the medicinal product. Besides, that sometimes the same device can take different products e.g. some inhalers and nebulizers. Proposed change (if any):	
216-219		Comment: EFA would like to highlight the **fundamental link between the SmPC and the Package Leaflet** for both integral and non-integral DDCs. Although the SmPC is procedurally aimed only at healthcare professionals, it should be made clear that it is the origin of all the information that is included in the Package Leaflet, and therefore arrives at the end users i.e. the patients. Unclear or insufficient information in the SmPC may have an impact in the Package Leaflet content, potentially putting patients' health at risk,	

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		especially in life-threatening situations such as during a severe asthma attack or an anaphylactic shock. EFA considers it is critical to ensure that SmPCs are designed for the market authorisation applications (MAAs) in the most accurate and comprehensive manner. This issue is essentially linked to health literacy, which should also be seriously taken into consideration. To prevent wrongful and potentially dangerous use/administration of a DDC, given instructions should be simple, readable, and –to the extent possible- supported by photos and videos. Drawings or other visual representations of the correct use of inhalers can also be helpful. Proposed change (if any):	
216-219		Comment: Now that EMA develops the basic principles for an electronic Product Information, it would be very useful for patients to access graphic information on how to use DDCs drawn from online sources. It is important that this information is **the result of a collective effort** involving healthcare professionals, the pharmaceutical industry, patients (patient associations such as EFA and patient experts as such, both at the EU and local level), but also interdisciplinary workers such as physicians, nurses, informal care givers should be taken into account, along with family members. Finally, organisations that support people with low health literacy need to be involved. Proposed change (if any):	

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216-219		Comment: EMA should put an effort in solving the issue of **contradictory leaflet information** in equal devices. There have been several cases in the past where package information did not match between similar products e.g. nasal sprays, inhalers. Furthermore, in some inhaler devices the leaflet information is different compared to the local protocols used by health care organizations, e.g. in the Netherlands. Proposed change (if any): Promote uniformity in leaflet information.	
220-225		Comment: As a general observation, apart from the package, EFA would see value in having **instructions on the device itself** e.g. 'shake/don't shake', 'keep upright', 'do not store in the bathroom' etc, possibly accompanied by illustrative pictures. This is because many patients do not read the leaflets but we also know that most patients make inhaler mistakes. Therefore, having some minor instructions on the inhaler might solve some problems in this respect. Given the rise of technology there are also **smart applications** to support these actions and also videos adapted to local circumstances. Moreover, providing some links for videos could also be considered, especially since they could prove useful to the family or care givers by involving them in training where other sources are not available. Also, EFA thinks that the package leaflet should contain detailed information on the parts of the device that are composed of or include allergen material e.g. latex. Proposed change (if any):	

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267-268		Comment: Sharps injury prevention features should be considered before and after using the device Proposed change (if any):	
276-291		Comment: In the CHMP recommendation on Adrenaline Auto-Injectors adopted in 2015 (EMA/465403/2015), EMA states that "Several factors may affect whether adrenaline reaches the muscle layer. These include: needle length, the skin-to-muscle depth, the way the auto-injector works (e.g. if it is spring loaded or not), the angle of placement on the skin and the force used to activate the device". In light of a constantly increasing rate of obesity in children and adult populations in Europe, it seems to be necessary to **consider functional performance of the devices in a holistic way**, taking into account the above-listed factors. Proposed change (if any):	
331-333		Comment: EMA should also take into consideration other **labelling technicalities** such as font size, letter emphasis etc. Proposed change (if any): For applied labels which include printed markings, the position of the label on the container should be specified and acceptable tolerances for the label positioning defined as critical in-process controls (IPCs) in Module 3.2.P.3.3 and Module 3.2.P.3.4. **Moreover, rules for other labelling technicalities,**	

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		including on font size and letter emphasis, should be defined.	
369-379		Comment: EFA would propose that stability studies should also look into the loss of functionality/stability **when there has been a bad use or bad process of maintaining and/or cleaning of the DDC.** Proposed change (if any):	
463-546		Comment: EFA would like to highlight the need to address the issue of **waste of devices** in the context of non-integral DDCs. For example, the package of dry-powder inhalers to treat asthma typically includes the medicine-containing canister, and the mouthpiece, likely made of hard plastic. However many non-integral DDCs used in respiratory disease are not sold alone, obliging patients not only to buy the whole set every single time they need the medicine, but also discarding a used mouthpiece that could be reused for a longer period of time. This, of course, requires clear and simple instructions on how to clean the device, but also the option to obtain a new device separately if the old one breaks down (see below). To avoid unnecessary waste, EFA recommends EMA to introduce waste-management considerations in the MAA, looking in particular into several points: ▪ The commercialisation of canisters separately (provided the development of agreements that make canisters eligible for reimbursement by national insurance schemes) ▪ Information on the usability period of a mouth-piece ▪ Clear instructions for the maintenance and sterilization of	

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		DDCs components to ensure safe re-use ▪ Information and waste disposal systems for discarded DDCs. ▪ Information on the recyclability and carbon footprint impact of the device, including the environmental burden of the drug delivery system Proposed change (if any):	
513-515		Comment: The **usability of the drug product** vis-á-vis the device in non-integral DDCs is another example of a discussion where patients can offer their experience-based input. EFA believes that EMA should offer clear statements towards this direction, ensuring patients' involvement. Proposed change (if any):	
543-546		Comment: EFA holds that the **design of medical devices and/or components** should in no case create any additional non-health burden to the patient resulting from their use. A specific case at hand is the (non-)electrostatic inhaling chambers, a key component of Metered Dosing Inhalers that are used in the management of respiratory diseases such as asthma. As opposed to non-electrostatic, the electrostatic ones typically require considerable cleaning after each use, creating a daily burden to users. At EFA we believe that the DDCs maintenance factors are issues that also need to be assessed in the quality requirements, and resolved through patient-centred	

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		actions in the product design process. Furthermore, the device needs to be robust so that **cleaning should not lead to an impairment**. For example, when washed in the machine, some chambers might have their rubber parts broken down, at the risk of being inhaled. Finally, throughout the process of product design, pharmaceutical companies should be knowledgeable of and compliant to national particularities for specific DDCs. For example, in some countries several DDCs are identified with a particular colour, clearly distinguishing them from another type or sub-type of the product. Lack of compliance to such a national practice might cause confusion to the patients, urging them to purchase the wrong product for the management of their disease. For example, there was an issue with a GSK inhaler that was produced in the wrong colour. Patients in some countries e.g. UK and Netherlands consider blue inhalers as bronchodilator and red inhalers as maintenance inhalers. GSK developed a blue maintenance inhaler which led to many problems. GSK therefore changed the colour of the inhaler. Proposed change (if any): DDCs like aero chambers should be designed in a way that makes swallowing the cap impossible. Moreover, the use of inhalers needs to be intuitive.	
643-652		Comment: EFA welcomes EMA's acknowledgement that the **advancement of science and technology for medical devices does not go hand in hand with the one for medicinal products**. This imbalance is an issue that lies at the heart of DDCs, as the	

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		compatibility between devices and drug products constitutes a vital factor for the DDCs efficacy and safety aspects. Especially in our disease areas, EFA patients witness extensive developments in the field of devices, exemplified by smart inhalers, air purifiers etc, without necessarily taking fully into account the progress in medicinal products. Although the advancement of technology and innovation is mostly beneficial, EFA thinks that the resulting asymmetry in the case of DDCs creates more immediate uncertainties for patients than solutions. A contributing factor in this respect is the **lack of adequate training of patients** into new and innovative device technologies, which would be vital, especially for patients with chronic conditions. We would therefore like to urge EMA to focus its efforts on preserving a healthy balance by promoting policies that help in bridging, rather than widening, the gap between the two. Moreover, we feel that EMA should propose a framework introducing patients into new and innovative devices, providing training in lay language in both physical and electronic forms, and ensuring the smooth transition from one device technology to the other. In particular, proposals should promote the simplification of administration of drugs (e.g. in the case of triple therapy), the use of less technical information and much clearer and more understandable text. Providing less technical information and much clearer and more understandable text would meet patients' needs and ensure safer administration of drugs. Proposed change (if any):	

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Please add more rows if needed.