EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Deadline for comments: 30 June 2017>

Submission of comments on *'Concept paper on the revision of the guideline on the pharmaceutical quality of inhalation and nasal products*' (EMA/CHMP/QWP/11577/2017)

Comments from:

International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS)

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)*
	We support the decision to update the guideline to reflect the scientific and technological advancements that are applied to inhalation and nasal product development. We recommend that the updates are not overly prescriptive, reference existing EU guidance and current compendia where possible, and recognise that alternate approaches may be possible with prior consultation and scientific justification	
	We support consistency of this guideline update with the proposed guideline on "Quality requirements of medicinal products containing a device component to delivery or use of the medicinal product," where applicable.	
	Discussions related to "patient handling studies" in 4.2.1.19 (of current guideline) should also make reference to current standards.	
	Increasingly, new add-on devices are becoming available (i.e., e-connective add-on devices for pMDIs). Some guidance on data requirements (if any) for those approved medicinal products that these add-on devices are to be used with would be welcomed.	
	Guidance on quality related data requirements for the addition of a Dose Indicator/Counter would be welcome	

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	as such guidance is currently not available. Principles outlined in similar guidance from other regulatory regions should be considered.	
	The guidance implies relevance to asthma and COPD inhalation products (indeed the clinical guidance for these diseases is cross-referenced). Consider including reference to other diseases treated using inhalation products	
	Are there plans to work with Health Canada on revisions to this guideline?	
	Consideration should be given to establishing requirements for pediatric subpopulations, in particular with respect to clinical use	

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)*
Section 2 Discussion (on the problem statement); first bullet		Proposed changes: <u>Dose Proportionality</u> Further clarification on how to demonstrate dose proportionality across a product range in vitro for waiving PK studies would beneficial and the general approach published recently provides a useful starting point (Quality of Medicines Q&A, Specific types of product - Orally inhaled products published 06/03/2017). <u>Stage Grouping</u> The use of impactor stage groupings is well established in the industry as part of the overall control strategy for inhalation products. The selection of stage groupings and flow rate, are product and patient group specific and therefore should be scientifically justified on an individual product basis. <u>Data for Inhalation Spray with Spacer/Holding Chamber</u> As detailed scientific discussion is available regarding requirements for in vitro assessment of spacer/holding chamber, we suggest that any revised guidance is provided at a high level only and reference other similar standards or guidance from other regulatory regions.	

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Section 2; second bullet		Comment: The document states that the revised Guideline will address *'the possibility to use new abbreviated methods for determination of aerodynamic particle size distribution'*. Proposed changes: We suggest that any guidance on this topic should not be prescriptive regarding when (for what purpose) the abbreviated methods are used, but that the possibility to use such methods for, e.g., determination of aerodynamic particle size distribution during development and during the commercial lifecycle be provided. To support this activity, description of suitable apparatus would be required and it is recommended that any such supporting information is established in the relevant pharmacopoeia, e.g., Ph. Eur. Inhalanda monograph. Please ensure that any guidance on abbreviated methods are aligned with or referenced in OIP equivalence guideline.	
Section 2; third bullet		Comment: This bullet states that a revised guideline would address, "The possibility to conduct intra-and inter-device variability for delivered dose uniformity in one test in the finished product specification." We support the combination of the determination of intra- and inter-device variability in one test for the assessment of delivered dose uniformity in the finished product specification.	

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		Any revised requirement for the intra and inter-device variability test should also be reflected in the Ph. Eur. Inhalanda monograph. Proposed changes: Consider providing examples describing sample regimens for the determination of the intra- and inter device variability; please also consider providing a definition of intra and inter-device variability.	
Section 2; fourth bullet		Comment: This bullet states that a revised guideline would address, *"Complementary guidance how to justify that the manufacturing process may be considered as a standard process in accordance with the process validation guideline."* We support the development of clear guidance on how the manufacturing process may be considered as a standard process as a key output of this update, as this will enable more rapid and consistent development of products and facilitate patient access; reduce the process validation requirements for MAA filings; and potentially impact on post approval submissions as a result of the data requirements not being as significant/stringent if a standard vs complex manufacturing process can be justified. Proposed changes: Providing complementary information on how to justify	

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		standard manufacturing processes for inhalation products would be beneficial to the industry. Such justification should be risk based and reflect the accumulated company knowledge of inhaled product platforms and their manufacturing unit operations, the site manufacturing experience for the specific product platform and the development knowledge (including product and process design space) available for the specific inhaled or nasal product. Please consider including guidance on where in module 3 such information should be placed.	
Section 2; fifth bullet		IPAC-RS will comment on this topic based on further regulatory developments related to the MDR and based on the proposed text in the revised guideline.	
Section 2; sixth bullet		Comment: The text states that revisions will address "*Updating of relevant parts to reflect the concepts of ICHQ8/Q9/Q10*." We support this alignment of the guideline with ICH Q8/Q9/Q10 concepts. The use of scientific and risk based approaches to both formulation development and device design and development, including the use of consensus quality standards such as the relevant ISO standards, are well established in the inhalation industry and the updating of relevant parts of the quality guideline to reflect ICH Q8/Q9/Q10 concepts at a high level would be beneficial.	

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Section 2; seventh bullet		Comment: The text notes that revision will address "*The possibility to include a chapter on lifecycle management.*" We welcome inclusion of a high level chapter on lifecycle management. Proposed changes: This chapter could provide guidance on the circumstances under which the provision of *in vitro* data may be used to support post approval changes, and of how risk based approaches, in alignment with ICHQ8/Q9/Q10, are applied to post approval change. Including case studies to exemplify the principles provided in the updated guidance for lifecycle management of changes typical for inhaled products would be helpful (e.g., how typical lifecycle changes such as container closure system updates, change of manufacturing site or process, introduction of a new product strength or pack size are documented with the existing variations guidance)	
Section 2 Discussion (on the problem statement); eighth bullet		Comment: Text states that the revised Guideline will address *'Inclusion of requirements in published Q&A, such as robustness test after dropping of an inhalation device and an acceptable range of fine particle dose (FPD) in the finished drug product specification'* Proposed changes: Clarifying robustness testing after dropping of an inhalation device would be helpful. The information provided in Quality of Medicines Q&A, "Should dropping of an inhalation device be	

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		investigated during development published June 2012" as well as existing standards should be considered. The inclusion of the requirements in published Q&A on the determination of an acceptable range of fine particle dose (FPD) in the finished inhaled or nasal drug product specification would be beneficial. We concur with the recommendation that ranges wider than ± 25% should be sufficiently justified *in vitro* and *in vivo*. We recommend that an acceptable FPD range needs to be product and device specific and linked appropriately to performance of batches used in Clinical Studies. The range should also take into consideration the test method variability and control of the appropriate fine particle fraction of the Aerodynamic Particle Size Distribution, i.e., reporting the sum of stages from an impactor is a more appropriate way of representing the respirable fraction as it avoids the potential error associated with interpolation from a cumulative mass graph as described by the Ph.Eur.	

Please add more rows if needed.