EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Deadline for comments: 30 June 2017>

Submission of comments on '*Concept paper on revision of the guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for the treatment of asthma in children and adolescents*' (EMA/CHMP/267194/2016)

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)*
	For new inhaler technologies please consider alignment among this guidance, the Pharmaceutical Quality guidance and the proposed guidance "Quality requirements of medicinal products containing a device component to delivery or use of the medicinal product." This is needed to avoid duplication or misalignment – with a proposal that the new guidance for devices provides the most specific information. The requirement for "user studies" should be defined in the proposed device guideline to ensure clarity of "clinical studies" versus "user studies" that do not have clinical endpoints	
	A section on lifecycle management is proposed in the concept paper on revision of the guideline on the pharmaceutical quality of inhalation and nasal products -- this is welcomed and a similar section could also be considered for the clinical OIP guideline update, addressing non-CMC issues, e.g., new labelling. The use of *in vitro* data only to support changes should be mentioned.	
	If more than one product pack size exists (e.g., number of doses in the device), guidance should be provided on the acceptability of bracketing the requirements (step 1-3).	
	Further clarification on how to demonstrate dose proportionality across a product range (difference doses) in vitro for waiving PK studies would be beneficial and the general approach published recently provides a useful starting point (Quality of Medicines Q&A, Specific types of product, Orally inhaled	

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	products published 06/03/2017). Similarly, further guidance on the optimal way to evaluate in vitro flow rate dependency with a view to using the outcome for waiving the need for PK data in patients would be beneficial	
	For paediatrics, therapeutic equivalence has been demonstrated based on *in vitro* data only. If *in vitro* data can be considered sufficient in these cases, this is welcomed and would be aligned with the Paediatric Regulation which aims to reduce unnecessary studies in the pediatric population	

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)*
Lines 49-54		Comment: We support the suggestion of considering the current difficulty in demonstrating equivalence between an older, variable reference device versus a newer, less variable device. Proposed changes: Demonstration of therapeutic equivalence using in vitro studies as the first step, should not be hindered by a Reference Product being variable; the equivalence statistics should be defined to reward more consistent Products. While the above suggestion was mentioned in Section 2 Problem Statement, there is no further discussion on this point in the next sections (i.e., Section 3) of this concept paper – considering the importance/impact of this issue, it would be crucial to address this in the new/revised guideline. The guidance should allow for justification of alternative acceptance criteria for in vitro equivalence, considering reference variance, providing that this has been adequately characterised.	

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Line 63-65		Comment: We support the suggestion of referring to full developments (e.g., innovator product) in the title of the guideline. Proposed changes: Please consider revising the guideline title to reflect application of the guideline to both innovator and generic products. Further, because the proposed framework poses that equivalence could be demonstrated on the basis of *in vitro* data alone, the title of the guideline should reflect this. Currently the title only references the 'requirements for clinical documentation' for therapeutic equivalence. Could the Agency also consider further clarifying the scope for the applicability of this guideline (beyond the name of the guideline).	
Lines 67-82		Proposed changes: Please provide more clarity on what is considered similarity in handling of different devices during step 1.	
Lines 73-74		Comment: Updates made on the requirements for representative batches, dose proportionality, flow dependency and stage groupings related to in-vitro studies, would be of	

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		interest. However, we would not support inclusion of more specific requirements, which would make demonstrating in-vitro equivalence more difficult.	
Lines 73-74		Comment: A Test Product with a lower flow rate dependency than the Reference Product should be acceptable given scientific justification; guidance could provide further information on what such justification might include.	
Lines 73-74		Comment: In Section 5.2 Known Active Substance of the OIP Guideline (CPMP/EWP/4151/00 Rev.1), the following is stated: *'The comparison should be performed per impactor stage or justified group of stages. At least 4 groups of stages are expected. Justification should be based on the expected deposition sites in the lungs.'* Proposed changes: As part of the revision of this guideline, can the Agency clarify the expectation regarding non-sizing fractions (e.g., Throat and Stage 0)? Is demonstration of equivalence required for non-sizing fractions?	
Lines 73-74		Comment: In Section 5.2 Known Active Substance of the OIP Guideline (CPMP/EWP/4151/00 Rev.1), the following is stated:	

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		'The maximum allowable in vitro difference should be indicated and justified, e.g. +/- 15% may be justifiable. Per impactor stage or justified group of stages the 90% confidence intervals for the observed in vitro differences must be calculated.' <u>Proposed changes:</u> There are multiple statistical approaches that could be used to meet these criteria. As part of the revision of this Guideline, could the Agency please provide further clarification on the exact requirements?	
Line 77		<u>Comment</u>: The text notes, "*In vitro data to support extrapolation of therapeutic equivalence from asthma to COPD or vice versa and to justify the use of healthy volunteers in PK studies, instead of patients, needs to be specified*." <u>Proposed changes:</u> Please clarify whether this is related to flow dependency? Otherwise, in which scenario would in-vitro data be different between the two indications?	
Line 80		<u>Comment</u>: This bullet states, '*Specific requirements on data with spacers need to be addressed.'*	

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		Proposed changes: Please consider referring to General Chapter <1602> on spacers and valved holding chambers that has recently become official in the United States Pharmacopeia when developing recommendations for the laboratory testing of these devices. There is no equivalent chapter in the European Pharmacopoeia.	
Lines 84 - 85		Proposed changes: In addressing the adequacy of using PK data to demonstrate similar efficacy and safety without the need for additional clinical data, it should be ensured there is clarity and detail associated with molecule dependencies, e.g., solubility, permeability.	
Lines 92-93		Comment: We would welcome guidance on alternative APSD grouping methods (variable confidence limits based on the reference product variability).	
Lines 92-95		Comment: We welcome further guidance on correction factors when demonstrating PK BE and the required IVIVC to support the proposal. We agree that this is important to address and both the elements of variability described need to be considered for their impacts on patients.	

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		<u>Proposed changes:</u> Variability in particle-size distribution between batches of the reference product or within a single batch of a reference product through their storage period should be justified on the basis of batches used in the clinical program. Overall, applying a correction factor implies there is a known correlation between *in-vitro* and PK. The correlation between these two variables is not established and may also be impacted by other variables, e.g., device differences. Any guidance must ensure the correlation factor is appropriately established and takes into account variability from product to product. Please also consider the following points when addressing this point in the updated guideline: • Please clarify if the IVIVC model relates PK outcome to aerodynamic particle size distribution. The concept paper currently states 'Particle Size Distribution'. • To include the acceptability of fine particle mass (FPM) instead of (A)PSD if it is shown to be a good predictor of PK outcome. • Please include guidance on how many batches of test and / or reference product would be acceptable for building the IVIVC model in order for the model to be considered reliable. • Please include guidance in the situation where there is no	

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		statistical interaction between product (test or reference) and *in vitro* parameter (e.g., FPM), that a common slope (but different intercept) model would be acceptable. • Include guidance that a correction factor can be applied to test only or reference only as appropriate, and it is not required to be applied to both products. • Please include further guidance on how the correction factor can be derived from an IVIVC model (and used in a study). The acceptability of pre-specifying a correction factor when demonstrating bioequivalence and the data to support such a proposal, e.g., *in vitro in vivo* correlation (IVIVC) need to be addressed, including the basis for establishing meaningful in vitro-PK correlation and the considering the impact of other variables such as the device	
Lines 104-105		Comment: The text notes that, "*Requirements for user studies on different inhaler devices and the required test panels (e.g., handling studies) should be addressed in more detail.*" Proposed changes: Would these requirements be covered by usability studies? If so, more details should be developed, that consider the Medical Device Regulation and other related existing guidelines, and standards.	

Please add more rows if needed.