30 May 2023

Submission of comments on 'Questions and answers on data requirements when replacing hydrofluorocarbons as propellants in oral pressurised metered dose inhalers' (EMA/CHMP/83033/2023) dated 30 March 2023

Comments from:

Name of organisation or individual
International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) International Pharmaceutical Aerosol Consortium (IPAC) European Federation of Pharmaceutical Industries and Associations (EFPIA)

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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EUROPEAN MEDICINES AGENCY
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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)*
	Within the Q&A document, there is mention that the data requirements can be reduced when sufficient data have been collected (Section 2, General Principles). How will companies know when the data requirements can be reduced when they are developing their products? How will it be visible that sufficient data on any novel inhaled propellant/excipient has been generated?	
	SAFETY: Could EMA clarify the situations where new safety studies may be needed to be conducted with active pharmaceutical ingredients (APIs)?	
	Could EMA establish some pathway to share safety information on new propellants, to avoid repeated studies and redundancies, thereby speeding up the transition?	

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 4-6		Comment: The document's title "*Questions and answers on data requirements when replacing hydrofluorocarbons as propellants in oral pressurised metered dose inhalers*" may need to be revised. One of the next-generation propellants with a low global warming potential is a hydrofluorocarbon (HFC 152a). Furthermore, certain pressurised metered dose inhalers (pMDIs) are intended for delivery to the nose. **Proposed change:** 'Questions and answers on data requirements when TRANSITIONING TO LOW GLOBAL WARMING POTENTIAL (LGWP) ~~replacing hydrofluorocarbons as~~ propellants in oral AND INTRANASAL pressurised metered dose inhalers'	
Line 38		Comment: In the text , '…of low global warning potential propellants (LGWP)…', there is a typo: 'warning' should probably be 'warming'. Also, the proposed abbreviation LGWP is confusing because 'P' in 'GWP' is typically used for 'potential' rather than 'propellant'. It would be helpful if the first mention of 'LGWP' included a reference to an authoritative source containing a formal definition and further details. . **Proposed change:** "…low global warming potential (LGWP) propellants". Please also include a reference to the definition of "low global warming potential", e.g., as specified in the F-Gas requlations and the KIGALI amendment of the Montreal Protocol.	
Lines 53-56		Comment:	

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		It is stated that "If a certain propellant has already been used in an approved medicinal product for the same route of administration, the data requirements for including the said propellant in another medicinal product can be reduced when sufficient data, including pharmacovigilance data, have been collected." **Proposed change:** For further clarity, suggest it be explicitly stated whether the active substance should be the same or whether the active substance can be different from that used in the approved medicinal product.	
Line 97		Comment: It is stated that "adequate manufacturing method validation and stability data should be provided." **Proposed change:** For companies that have manufactured MDIs for many years, the manufacturing process is considered a standard process, therefore manufacturing method validation data should not be required.	
Lines 97-100		Comment: It is stated that 'Stability data for at least two batches, packed in the commercial container closure system, stored at long-term conditions and in different orientations for a sufficient time should be provided to conclude similar stability profile.' **Proposed change:** Please consider allowing minor changes to the container closure system for commercial supply chain if the changes can be justified as not being quality critical. Also, please consider allowing alternative approaches to the stability data package if justified based on an appropriate risk assessment.	
Lines 101-102		Comment:	

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		It is stated that 'Stability data for the new propellant in other finished products could be seen as supportive.' **Proposed change:** Change to 'Stability data for the new propellant in other finished products ~~could~~ *would* be seen as supportive.'	
Lines 107-115		Comment: Propellants are volatile (i.e., rapidly dissipating) gases, which makes nonclinical in vitro studies [per ICH M3(R2)] practically challenging to conduct and may not provide reliable results. **Proposed change:** It would be helpful if this could be acknowledged in Section 3.2. and give the applicant scope to provide adequate justification to waive such studies.	
Lines 107-115, 172-175		Comments: Would toxicology data from the manufacturers of the propellants be sufficient or does the product developer also need to do tox.studies with the novel excipient? Are environmental non-clinical studies required? Is it a safety study of the novel propellant alone, or of the drug product including both propellant and API? Section 3.2 only references the testing of the propellant alone. **Proposed change:** Please provide clarification. Please also provide some general considerations for when a bridging toxicology study for a drug product may be needed (and timing of this study) and incorporate this into Figure 1 of the stepwise schematic.	
Lines 112-115		Comment: The sentence in lines 112-115 seems to refer to excipients yet ends with '…as for any new substance.' **Proposed change**	

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		Put a full stop after '…ICH M3 (R2)'. Delete 'as for any new substance'.	
Lines 122-128		Comment: Regarding Section 3.3 (a) Data on ciliary function. As noted, there is currently no accepted method to directly assess the potential of a drug or chemical to impact mucociliary clearance. Conventional safety studies may indirectly indicate whether the test article induces significant treatment-mediated effects on mucociliary clearance. Standard evaluations of clinical signs (such as increased cough) or increased respiratory disease may be used as a surrogate marker for treatment-mediated effects on mucociliary clearance. **Proposed change:** Observation and comparison of clinical signs and symptoms (such as cough, increased respiratory disease) during a clinical safety study using the proposed formulation **or** propellant-only is sufficient evidence for lack of treatment related effects on ciliary function.	
Lines 129-135		Comment: Regarding Section 3.3 (b) Airway sensitivity reactions. Supportive data for possible bronchoconstrictive effects would be attainable during a safety study (see line 138 "The main objective of this study is to collect adverse events such as bronchoconstriction, hoarseness, and cough"). **Proposed change:** Propose that a standalone airway sensitivity study would only be required if safety studies suggested propensity for the new propellant to increase risk of bronchoconstriction.	
Line 139		Comment: It is stated that 'Study duration should be at least 3 months.' Adverse events such as bronchoconstriction can be evaluated even within a shorter study as bronchoconstriction usually occur during the first administration or within one week.	

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		Proposed change: Given the short half-life of SABA medications and the frequency of patient usage, if a sufficient number of adverse events could be collected in a shorter time period, could a shorter duration be possible? Suggest including in the Q&A document a statement '**Other study designs could be acceptable if suitably justified'.**	
Lines 141-143		Comment: '*The pMDI product at investigation should ideally be a vehicle version of the final formulation to allow detecting adverse effects of the novel propellant while minimising the risk that these are masked by the active substance(s) (thereby compromising any extrapolation of the conclusions to other products).'* Statement and wording 'vehicle version of the final formulation' is confusing and not clear. As indicated in the parenthesis the extrapolation of the safety study results to other products with the same propellant seems to be intended. Hence the following is proposed: **Proposed change:** '*The pMDI product at investigation should ideally be a formulation without active substance to allow….'*	
Lines 149-152		Comment: It is stated that 'it would be acceptable to use a final finished product formulation indicated for daily maintenance treatment, preferably a mono-component product such as a glucocorticoid.' **Proposed change:** Can final finished product formulation also be used in the safety study if it is indicated for rescue treatment (for example, a short acting bronchodilator?). Given that well-controlled asthma patients on a daily maintenance regimen of inhaled corticosteroid monotherapy would have little need for SABA reliever medication, and thus may receive insufficient	

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		investigative product exposure in a safety study, could regular scheduled SABA use be implemented, to support development of SABA with novel propellant, regardless of symptoms? Given that asthma patients across different levels of severity use SABAs for relief, could well-controlled patients on dual inhaled therapy (ICS/LABA) and triple inhaled therapy (ICS/LABA/LAMA) be included?	
Lines 153-154		Comment: It is stated that, 'A comparator product which is an approved pMDI product supported by a full dossier should be included.' **Proposed change:** Since considerable adverse event data already exists for SABA medications, could a single arm safety study utilizing only the investigative SABA formulation be conducted with an adverse event profile compared to existing historical SABA data? If historical data is acceptable, what data sources could be utilized to derive the baseline incidence of the adverse events to be studied, and thus, subject numbers?	
Line 167		Comment: This is the first mention of a step-wise approach. The text does not follow the flow diagram. **Proposed change:** Introduce this step-wise approach earlier in the text and insert a more detailed flow diagram earlier in this document as well.	
Line 168		Comment: The sentence 'Data should be provided both with and without spacer/holding chamber.' presumes that a spacer/holding chamber must be used. Not all products are supplied with a spacer and not all strengths of a particular product supplied with a spacer	

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		Proposed change: Recommend updating the sentence as follows: *'Data should be provided both with and without spacer//holding chamber* ***where applicable '***	
Line 174 (Figure 1)		Comment: It would be useful to include if / when clinical safety & other studies should be conducted when in vitro equivalence is demonstrated. The schematic only speaks to in vitro, PK, and PD studies. **Proposed change:** Please clarify whether the schematic is only applicable to novel excipients? Is it appropriate to enhance the schematic to also speak to if / when clinical safety & other studies should be conducted when in vitro equivalence is demonstrated.	
Figure 1, Step 2		Comment: Step 2 in the flow diagram could be misinterpreted **Proposed change**: Add "of the API" to the first parenthesis, so it would read "(total exposure of the API)".	
Figure 1, after Step 2		Comment: '*Are test and reference product therapeutic equivalent by means of PK data…*?' It should be clarified that for the PK safety study demonstration of non-inferiority rather than equivalence (i.e. not higher systemic exposure for the test product than for the reference product) is sufficient (in line with EMA PK working party Q&A section 3.4). Clarification could be included in Step 3 as proposed below. **Proposed change:** "*If the PK safety study failed to demonstrate not higher systemic exposure for the test product than for the reference product for any active substance, …*"	

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Figure 1, after Step 3		Comment: Wording included in the last arrow is not accurate and hence we propose a change to indicate that evidence can also be split between efficacy and safety / PK and PD. **Proposed change:** '*PK and/or PD data'.*	
Line 183		Comment: The sentence '……lung deposition / local availability with and without spacer need to be provided' presumes that a spacer must be used **Proposed change**: Recommend updating the sentence as '*……lung deposition / local availability with and without spacer need to be provided where applicable* '	
Lines 199 - 217		Comment: The Q&A document states 'The conclusion from studies supporting safety of a novel propellant as outlined in question 3.3. above can be extrapolated to children and adolescents even though the studies are conducted in adults only.' **Proposed change:** Does this also apply to any clinical safety or other studies conducted in asthmatic adults? Please clarify.	
Line 213		Comment: Wording "*it might be acceptable*" is not very clear as to what is required, i.e., would additional in-vitro studies be sufficient?	

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		Proposed change: Please provide examples so it is clear when it would and would not be acceptable to keep the age limit.	
Lines 222-227		Comment: Regarding the statement: *'Inclusion of statements such as 'HFC free' on the label: As a general principle, the Summary of Product Characteristics (SmPC) is the basis of information for healthcare professionals on how to use the medicinal product safely and effectively. There is no ground or need to include additional information on elements which are not included in a medicinal product (i.e., absence of a component in the product or in a container), as the information may become extensive and confusing. Therefore, such promotional statement is not allowed'.* **Proposed change:** It is important that information about the environmental benefits of the reformulated product is visible to HCPs and patients in order to drive the pace and level of change required to meet the environmental goals of the F-Gas legislation. Without this prescribing behaviours will not be challenged/updated resulting in a slow uptake, reduced urgency for the supply base to change and ultimately a slower reduction of targeted emissions from pMDIs.	

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