EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 March 2023
EMA/CHMP/83033/2023
Committee for Medicinal Products for Human Use (CHMP)

Questions and answers on data requirements when replacing hydrofluorocarbons as propellants in oral pressurised metered dose inhalers

Agreed by Rheumatology and Immunology Working Party	February 2023
Adopted by CHMP for release for consultation	30 Mar 2023
Start of public consultation	April 2023
End of consultation (deadline for comments)	31 May 2023

Comments should be provided using this template. The completed comments form should be sent to QAspropellants@ema.europa.eu

Keywords	question and answer, oral pressurised metered dose inhalers, hydrofluorocarbon replacement and propellant

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1. Introduction

There is an increased awareness about the global warming potential of certain hydrofluorocarbons (HFCs) used as excipients (propellants) in pressurized metered dose inhalers (pMDIs). Therefore, the European Commission has taken an initiative aiming at phasing out the use of HFCs in pMDIs in favour of low global warning potential propellants (LGWP). Additionally, companies have taken initiatives towards replacing the existing propellants with LGWPs by asking for scientific advice on product development. As such, propellant replacement constitutes a major change to the finished product formulation with potential impact also on the construction of the inhaler; therefore, data confirming maintenance of adequate finished product performance need to be provided for each modified product. In addition, data addressing possible toxicity and local tolerance of novel propellants need to be provided. This questions and answers document aims at providing advice regarding data requirements for such replacements. It applies to all medicinal products irrespective of the legal basis for marketing authorisation.

2. General principles

Propellants could be introduced in a medicinal product either as part of an initial marketing authorisation application (approved via either full or abridged applications), as a part of an extension application or as replacements of existing propellants via a variation procedure for an approved medicinal product. The data requirements depend on whether the propellant is regarded as novel (i.e., not previously used in any approved medicinal product with the same route of administration) or established. 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.

When documenting a formulation with a novel propellant, there are two aspects to cover pertaining to the efficacy and safety of the product, i.e., issues related to the safety/tolerance aspects of the novel propellant (see question 3.3) and changes to the formulation with impact on the aerodynamic particle size distribution of the active substance in the product as well as on other properties of the emitted cloud. The latter point might have clinical implications as the local and systemic exposure of the active substances could be impacted as discussed in question 3.4. below and needs to be addressed for all product formulations also in case of established LGWPs.

3. Questions and answers on data requirements when replacing hydrofluorocarbons as propellants in oral pressurised metered dose inhalers

3.1. What are the quality data requirements?

When replacing the propellant in a medicinal product, quality data should be provided as for any other variation or extension application.

With regards to the control of excipients (propellant), in case of novel propellants, full details should be provided as outlined in the Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product (EMEA/CHMP/QWP/396951/2006), under the section novel excipients. For an established LGWP section 3.2.P.4 should be provided as standard; of note, a specification, including relevant tests, e.g., identification, physical characterisation (e.g., boiling point, vapor pressure, relative density), appearance, assay, acidity, total residue, moisture content, related

impurities and unrelated impurities (e.g., CO, N_2, O_2), is needed. However, a change of propellants may have a significant impact on the finished product functionality and performance and the following quality data requirements are to be taken into account:

- All relevant pharmaceutical development studies described in the Guideline on the pharmaceutical quality of inhalation and nasal products (EMEA/CHMP/QWP/49313/2005 Corr).
- For all the indicated patient populations, propellant aspects which may impact the usability of the product such as expelling pressure, taste, feeling in the mouth and flammability.
- Re-evaluation of the finished product specifications, at release and at the end of shelf-life, in view of the results of the batches used in the studies pivotal for demonstrating therapeutic equivalence and safety, and proposed in line with the finished product specification(s) section for inhalation products described in the Guideline on the pharmaceutical quality of inhalation and nasal products (EMEA/CHMP/QWP/49313/2005 Corr). When no clinical studies have been conducted, the critical quality attributes limits should not be substantially changed.
- Discussion and justification of device related changes (e.g., in the device components such as valve and canister), taking into consideration the requirements described in the Guideline on quality documentation for medicinal products when used with a medical device (EMA/CHMP/QWP/BWP/259165/2019) and related documents.
- Pressurised metered dose inhalers are considered as a critical dosage form. Hence, adequate manufacturing method validation and stability data should be provided. 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. The batches should preferable be of production scale, however, pilot scale may be sufficient, if justified. Stability data for the new propellant in other finished products could be seen as supportive.

In addition to characterisation of the finished product with the new propellant, *in vitro* data should be used as the first step to establish therapeutic equivalence between the reformulated product and its reference, see question 3.4.

3.2. What are the non-clinical data requirements?

Excipients are not expected to have any intended pharmacological activity; therefore, primary and secondary pharmacology studies are not warranted. Consequently, the non-clinical requirements for a novel excipient are limited to toxicology and pharmacokinetics. Safety pharmacology data might be obtained in toxicology studies obviating the need for stand-alone safety pharmacology studies. However, a lack of these data needs to be justified.

Full details as outlined in the Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product (EMEA/CHMP/QWP/396951/2006) should be provided and adequate non-clinical data in accordance with ICH M3 (R2) as for any new substance. To support the use of novel excipients in a paediatric population (question 3.5.), ICH S11 may also apply.

3.3. What are the data requirements to address safety/tolerance aspects of a novel propellant?

3.3.1. Data requirements on local tolerance

Data on the local tolerance of the propellant alone (without active substances involved) should be generated by two studies:

a) Data on **ciliary function** should be preferably collected from a study in non-smoking healthy volunteers as this is deemed the most sensitive population to detect differences between the new and the reference propellant. There is no established and validated "golden standard" method (currently, April 2023) and thus a thorough justification for the choice of the design is needed. A scintigraphy evaluation would be an acceptable option if statistical aspects such as pre-specification of a primary endpoint with a non-inferiority margin at a relevant level can be justified.
b) Data on possible **airway sensitivity reactions** should be collected by studying lung function in asthmatic patients. A cross-over design using a supratherapeutic propellant dose is recommended where FEV1 (AUC0-15min) is investigated. A younger population may be more sensitive to detect bronchoconstrictive effects, hence an upper age limit of, e.g., 45 years is advised. As possible effects of the chosen comparator propellant might not be known, it is recommended to conduct a pilot study to support the choice of the study size and of the non-inferiority margin.

3.3.2. Data requirements on clinical safety

The clinical safety of any novel propellant should be supported by at least one safety study. The main objective of this study is to collect adverse events such as bronchoconstriction, hoarseness, and cough. Study duration should be at least 3 months. A study size of approximately 300 subjects in each treatment arm would allow an adequate estimation of common adverse events.

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). For instance, bronchoconstriction could be masked by β_2-agonists and hoarseness and cough are known side effects from glucocorticoids, complicating the evaluation. The subjects to be included could then be either healthy volunteers or patients (who are else using dry powder devices for maintenance treatment).

Nevertheless, as 3-month studies investigating an excipient might prove difficult to conduct in practice, 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. The included subjects should preferably have a low risk of need for concomitant treatment (besides reliever medication, which needs to be allowed).

A comparator product which is an approved pMDI product supported by a full dossier should be included. This could, e.g., be a pMDI product for which the marketing authorisation is intended to be varied (or a placebo version of the same).

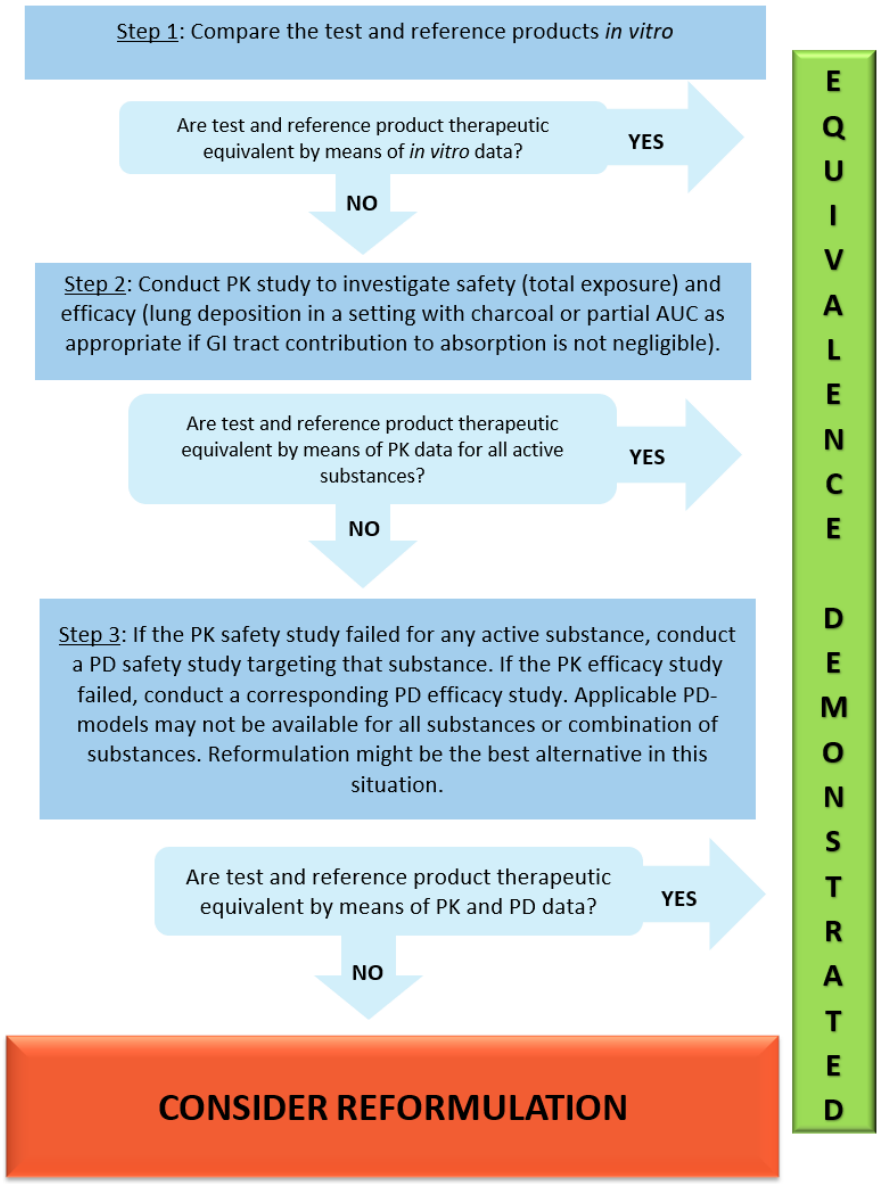
As the amounts of a propellant included in the medicinal product (referring to daily exposure) might be of relevance for the safety profile, in the case that the study is conducted with a medicinal product containing an active substance, it is recommended to choose a product/strength where the number of actuations needed is in the higher range.

3.4. What are the data requirements to address possible changes to the exposure to the active substance(s)?

For each strength of the pMDI product for which the marketing authorisation is to be varied due to a change of propellant, data must be provided showing that the local and systemic exposure of the active substance(s) is not impacted by the change. Therapeutic equivalence should be confirmed as outlined in the guideline on the requirements for clinical documentation for orally inhaled products (OIP) (CPMP/EWP/4151/00 Rev. 1) with related documents. This guideline is under revision, and it should be interpreted as a stepwise procedure to establish therapeutic equivalence between two products as outlined in Figure 1 below. Data should be provided both with and without spacer/holding chamber.

For hybrid or generic medicinal products, the comparator product should be the reference medicinal product irrespective of the propellant used in the said reference medicinal product.

Figure 1 Schematic overview of the three-step approach for showing therapeutic equivalence for orally inhaled products.



3.4.1. Step 1 – *In vitro*

All pharmaceutical requirements specified in the Guideline on the requirements for clinical documentation for orally inhaled products ((CPMP/EWP/4151/00 Rev 1) section 5.2 should be evaluated for the modified product. Data should be provided irrespective of whether all criteria are fulfilled or not.

3.4.2. Step 2 – Pharmacokinetics

In the case that therapeutic equivalence cannot be established based on *in vitro* data, PK data to address systemic safety and lung deposition / local availability with and without a spacer need to be provided. As surrogate marker for safety, total exposure (AUC_{0-t} and C_{max}) should be used. For products where the contribution from the gastrointestinal tract to the systemic exposure following inhalation is negligible (<5%), the systemic safety study could also be used to compare lung deposition. In the case that the contribution from the gastrointestinal tract is not negligible, local

exposure as a surrogate marker for efficacy could be either exposure (AUC_{0-t} and C_{max}) following charcoal administration or (in case of rapidly absorbed substances) $AUC_{0-30\ min}$ (together with C_{max}).

3.4.3. Step 3 – Pharmacodynamic data

In the cases where comparable local and systemic bioavailability between test and reference products cannot be confirmed, concerns about efficacy and/or safety raised due to the differences recorded could be addressed with targeted PD studies. It is acknowledged though that it is difficult to design such studies with adequate assay sensitivity and for some substance/combination of substances adequate PD models are not available. Therefore, it is recommended to make a request for scientific advice before conducting any PD study. The possibility of reformulation could be considered in the case that comparable local and systemic bioavailability with and without charcoal (as applicable) cannot be confirmed.

3.5. What are the data requirements for children and adolescents?

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.

If, with reference to question 3.4, therapeutic equivalence between the test product and its reference is confirmed at step 1 (i.e., *in vitro* data only), the same age limit as for the reference product can be applied.

It is also acceptable to extrapolate the conclusion on therapeutic equivalence demonstrated by pharmacokinetic (and if applicable pharmacodynamic) studies in adults to adolescents as long as the reference product is approved for this age group.

According to the guideline on the requirements for clinical documentation for orally inhaled products (CPMP/EWP/4151/00 Rev 1), extrapolation of pharmacokinetic (and if applicable pharmacodynamic) data in adults to children would not be straight forward as small differences between products that are not detected as a difference in exposure in adults could still be of concern in children due to the smaller size of their airways and their different breath pattern. Nevertheless, it might be acceptable to keep the age limit currently approved for the product subjected to the change of propellant also, in the case that therapeutic equivalence is established based on PK data in adults, i.e., in the absence of specific data in children, because retained positive benefit/risk balance in this population is anticipated.

3.6. Are there any specific considerations related to the product information following a change in propellant?

Name of the product: changes in the qualitative composition of excipients do not require any change in the name of the product.

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.

Flammability warning: Depending on the propellant and product formulation, a warning on flammability may be necessary. Inclusion of warnings on use near an open flame, lit cigarette or some devices (e.g., hairdryers) should be considered. In accordance with the European Commission Guideline on Summary of Product Characteristics, any warning necessary for excipients should be included in the SmPC at the end of section 4.4. The warning should also be reflected in section 2 of the package leaflet under <X contains {name the excipient(s)}>.

Special storage conditions: Any subsequent special storage conditions should be reflected in section 6.4 of the SmPC, section 9 of the Annex IIIA – Labelling, and section 5 of the package leaflet.