30.06.17

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:

| Name of organisation or individual |
| --- |
| EFPIA – Sandra Rodrigues (sandra.rodrigues@efpia.eu) |

*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).*

1. General comments

| Stakeholder number*(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)*(To be completed by the Agency)* |
| --- | --- | --- |
|  | EFPIA welcome the revision of the existing Orally Inhaled Products (OIP) guideline and fully support the need to provide clarification on clinical data required to document the therapeutic equivalence between two inhaled products for the treatment of asthma in children and adolescents and chronic obstructive pulmonary disease in adults.In addition to the detailed comments displayed in section 2 of this document, we have the following general consideration for the revised guideline:1. **Step-wise approach to demonstrate therapeutic equivalence:** EFPIA recommends that the guideline should clearly differentiate between variations of an approved product and the development of a new product. For changes to existing products, the formulation and the inhaler have been known for years and significant data, including *in vitro*, PK, PD, Human Factor data and pharmacovigilance data have been collected pre- and post-product approval. This situation does not necessarily apply to ‘generics’. Therefore, EFPIA suggests the need to consider different approaches when demonstrating therapeutic equivalence:
* For changes to approved products, the use of *in vitro* data alone, or *in vitro* and PK data as allowed in the current version of the guideline, may be sufficient provided justification.
* For the development of ‘generic’ products submitted as hybrid applications, *in vitro* and/or PK on their own may not be sufficient to demonstrate therapeutic equivalence.
1. **Global harmonisation:** Knowing products are usually developed globally a harmonised regulators’ position would be welcome.
2. **Bracketing the requirements:** 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).
3. **Clarifications for waiving PK data:** Further clarification on how to demonstrate dose proportionality across a product range (different 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 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.
4. **Reference to the PKWP Q&A should be considered:** The revised guideline should implement the PKWP positions summarised in the [Q&A document](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000072.jsp) EMA/618604/2008 Rev. 13 (“Questions & Answers: positions of specific questions addressed to the Pharmacokinetic Working Party (PKWP)”), specifically under chapter 17, Evaluation of orally inhaled products.
5. **Proposal to modify the title of the revised guideline:** It is noted that there is not a proposed revision of the title of the guideline. Given that equivalence could be demonstrated based on *in vitro* data alone, though acknowledging this is challenging, ideally the title of the guidance should reflect the basis on which a test product could be approved. Currently the title only references the ‘requirements for clinical documentation’ for therapeutic equivalence.
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1. 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)* |
| --- | --- | --- | --- |
| 41-42 and 97-99 |  | **Comment:** Even if assay sensitivity can be demonstrated, the dose-response may be so weak that a formal RDP analysis is difficult. Moreover, the current guideline has a vague expression regarding Relative Dose Potency: “*The acceptance criteria for relative potency should lie entirely within 0.67 to 1.5*”. It is not clear that this refers to a 90% confidence interval.**Proposed change (if any):** The condition for the RDP analysis should be clarified. Moreover, attention should be paid to the situation with a weak dose-response. Alternative criteria might address only comparisons on the efficacy scale. |   |
| 49-51 |  | **Comment:** It is proposed to add mist inhalers to DPIs and pMDIsas these forms can also be useful and possibly developed. |  |
| 63-65 |  | **Comment:** It would be useful to know to which extent the guideline could apply to possible scenarios happening during product development, eg to bridge between two inhalation drug products during clinical development |  |
| 67-82 |  | **Comment:** Criteria on pharmaceutical equivalence reported in CPMP/EWP/4151/00 and EMEA/CHMP/QWP/49313/2005 are not superimposable, alignment would be a welcome addition.More specifically, as part of the criteria included in section 5 of the current guideline, and which must be met to claim similarity, there is the following one:* The pharmaceutical dosage form is identical (e.g. pMDI, non-pressurised MDI, DPI, etc.).

More clarity on what is similarity in handling of different devices during step 1 would be welcome, eg device testing.. |  |
| 71-76 |  | **Comment:** While the specific in vitro criteria may not be sufficient to demonstrate therapeutic equivalence, they are relevant and should be assessed in the context of the totality of the data, including PK and PD data as relevant for the product in question, to establish therapeutic equivalence |   |
| 71-74 |  | **Comment:**Criteria to establish appropriate stage groupings should be more clearly described. In particular, it should be clarified how to address the difference in cut-offs of the stages at different flow rates and acceptability of using groupings based on absolute size fractions (e.g. 3-5mcm), rather than impactor stages.**Proposed change (if any):**To ensure consistency in the cut-offs selected for groupings across different flow rates, it is proposed to allow selection of groupings based on size fractions (extrapolated by the cumulative undersize distribution) |  |
| 7392-95 |  | **Comment:***Given the inherent and well known intra and inter batch variability of inhalation products, selection of the Test and Reference batches for a formal in-vitro bioequivalence study should not be random but rather based on a careful assessment of their representativeness of the “median product quality”.*Reference product should be characterized *in vitro* (i.e. FPM) to profile its “quality distribution”.Test product batches should be produced introducing as much variability as possible in terms of raw materials critical quality attributes (e.g. API PSD) to provide a basis for raw material and finished product specification setting.**Proposed change** taken from EMA Q&A on quality <http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000072.jsp&mid=WC0b01ac058002c2b0#section8>The batch(es) of the comparator used in clinical studies should be representative of the commercial batches available on the market, including consideration for different ages or shelf-life of the product. The test product has to be representative of future batches and therefore the specification limits are critical to ensure similar characteristics even at the end of the shelf-life.How the representative batch(es) is chosen should be fully discussed and justified in the dossier, preferably in Module 3.  |   |
| 71-76 |  | **Comment:**Guidance on how to evaluate and process in-vitro data to prove therapeutic equivalence between two inhalation products is lacking in the current version of the guideline.**Proposed change (if any):**Provide clear and detailed explanation on how to process data to perform an in-vitro bioequivalence study. Explanation can be provided in a dedicated annex. Acceptability of Population BE or Average BE approaches should be clearly stated, including acceptability and/or need of data transformation (e.g. log-transformation for Average BE approach). |  |
| 77 |  | **Comment:**Can it please be clarified whether this is related to flow dependency? Otherwise, in which scenario would in-vitro data be different between the two indications?**Proposed change (if any):**To be clarified in revised guideline |  |
| 80 |  | ‘*Specific requirements on data with spacers need to be addressed’***Comment:** While we welcome this intent, we expect that consistency with the ‘Quality requirements of medicinal products containing a device component for delivery or use of the medicinal product’ (EMA/CHMP/QWP/BWP/661488/2016) guideline, which is due for revision, will be ensured. |   |
| 84 - 85 |  | **Comment:**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. |   |
| 91  |  | ‘Requirements for PK data on spacers and nebulisers should be reviewed’.**Comment:** We welcome this proposed revision since spacer and nebulisers have been shown to be useful in some specific patients’ populations and circumstances. When needed, PK with the spacer should be studied for the new product to ensure that the interaction between the device and spacer can be reproduced. |   |
| 92-95 |  | **Comment:**IVIVC for OIPs is currently not well established and no specific guideline is available. Nevertheless, impactor testing of OIPs is nowadays recognized as a very reliable and powerful tool able to characterize and discriminate the APSD of aerosols generated by OIPs. In case any APSD parameter (e.g. fraction <5mcm, fraction <3mcm) is found to have a correlation with in-vivo PK parameters (i.e. AUC, Cmax), it is considered sensible to use this in-vitro “predictor” to potentially introduce a correction factors that accounts for the Reference and Test product inherent variability (intra-, inter-batch and stability-related).Arguably, even when no strong IVIVC correlation can be established, in-vitro predictor could still be proposed based on biopharmaceutical considerations related to the specific API.**Proposed change (if any):**Clarification should be provided on the pre-requisites to allow implementation of a correction factor as well as procedure to calculate it. Moreover, minimum requirements to declare an acceptable IVIVC would be welcome. Internal and/or external predictability acceptance criteria for the IVIVC model should be defined (e.g. 10% on average prediction error, 15% on individual prediction error; in line with “Guidance for Industry - Extended Release Oral Dosage Form: Development, Evaluation and Application of In Vitro/In Vivo Correlations September 1997”). |   |
| 97-99 |  | **Comment:** When studying inhaled corticosteroids the current guideline (p.15) states that in bronchoprotection studies each dose should be given via each device during at least 4 weeks. This makes the total study time very long in a cross-over study. The dose-response in bronchodilatation may be too weak to make that a useful alternative.**Proposed change (if any):** Discuss alternative design optionsfor cross-over studies (shorter treatments, ascending doses without washout) |    |
| 102 - 103 |   | ‘*Recommendations are needed as to whether pharmacodynamic data obtained in healthy volunteers can be used to show therapeutic equivalence*’.**Comment:**We support that recommendations are needed and would highlight that a cautious approach should be taken in recommending that PD data from HV are a suitable alternative for patient PD. For example, considering the limited ability of healthy volunteers to demonstrate a response for this reason the methods would likely lack the ability to discriminate between test and reference products. |   |
| 104-105 |  | ‘Requirements for user studies on different inhaler devices and the required test panels (e.g. handling studies) should be addressed in more detail. **Comment:** We support this proposed revision considering that device robustness and patient usability should be addressed in appropriate usability studies, and as part a clinical trial.  |   |

Please add more rows if needed.