EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

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.

Agreed by Respiratory Drafting Group	October 2016
Adopted by CHMP for release for consultation	23 February 2017
Start of public consultation	22 March 2017
End of consultation (deadline for comments)	30 June 2017

The proposed guideline will replace ' 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 use in the treatment of asthma in children and adolescents' (Doc. Ref. CPMP/EWP/4151/00 Rev. 1).

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

Keywords	therapeutic equivalence, asthma, COPD, orally inhaled

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1. Introduction

This concept paper concerns a revision of the guideline directed to the requirements for demonstration of therapeutic equivalence between two inhaled products. The guideline focuses on hybrid applications but may be applicable also for other applications that are based on demonstration of therapeutic equivalence compared to a reference product, such as line extensions and variations. The guideline was originally published in September 2000 and was revised between September 2007 and January 2009 (henceforth referred to as Revision 1).

2. Problem statement

Since the last revision, several MAAs with the aim to demonstrate therapeutic equivalence compared to a reference product concerning orally inhaled products have been submitted for regulatory review to the National Competent Authorities. The proposed revision is aimed at updating the guideline to reflect knowledge gained from regulatory experience.

Demonstration of therapeutic equivalence of two orally inhaled products moves in a stepwise fashion from *in vitro* studies (step 1), to pharmacokinetic studies (step 2), to pharmacodynamic and clinical safety/ efficacy studies (step 3). This should be clearly described in the revised guideline. *In vitro* aspects relevant for the establishment of therapeutic equivalence are described in this guideline but reference is also given to the Guideline on Pharmaceutical Quality of Inhalation and Nasal Products (EMEA/CHMP/QWP/49313/2005).

Establishing therapeutic equivalence based on *in vitro* data only has proved to be difficult. Also, showing therapeutic equivalence based on PD/clinical data is challenging because of difficulties in ensuring assay sensitivity. Pharmacokinetic studies seem to be simpler, shorter and more discriminative in order to demonstrate similar efficacy and safety without the need for additional clinical data. These aspects should be reflected in the revised guideline.

In addition, during the review of applications based on the requirements given in Revision 1, a number of issues were discussed with regard to choice of batches, strengths and study population in pharmacokinetic studies. The principles that were established need to be included in the revised version.

Since Revision 1 was published, there have also been advances in inhaler technology of pressurised metered dose inhalers (MDI) and dry powder inhalers (DPI) resulting in better drug delivery characteristics. Also, nebuliser technology has advanced with the development of smaller and more portable devices. Demonstration of equivalence between a consistently performing new device (which is desirable) and a more variable but established device is challenging. This may have an impact on the development needs, which need to be considered.

Few products have been approved in children based on the current requirements to demonstrate therapeutic equivalence in the paediatric population. For most of these products, the demonstration of therapeutic equivalence was based on *in vitro* data only. This indicates that the clinical data requirements in paediatrics as detailed in the guideline might be difficult to comply with. Thus, requirements for different paediatric age groups should be reviewed and, if appropriate, revised.

3. Discussion (on the problem statement)

The following items have been identified and would need to be addressed in the revised guideline:

General comments:

- Despite the emphasis in the document on hybrid/abbreviated developments, the name of the guideline as well as some sections refer to full developments. The name of the guideline should be adapted accordingly.

In vitro equivalence studies (Step 1)

- The Guideline referred to in this concept paper and the Guideline on Pharmaceutical Quality of Inhalation and Nasal Products (EMEA/CHMP/QWP/49313/2005) are written to complement each other and should always be read in conjunction. The criteria for pharmaceutical equivalence should thus be in line with corresponding requirements in the pharmaceutical guideline.
- The use of only comparative *in vitro* data (Step 1) may be considered acceptable if the product satisfies all of the criteria (compared with the reference product) as laid down in the guideline. However, specific requirements on representative batches, dose proportionality, flow dependency and stage grouping are not well described in the current guideline. In addition, these aspects are important to support the PK studies. Thus, specific information on these aspects could be included in the revised guideline as appropriate.
- *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, need to be specified.
- Specific requirements on data with spacers need to be addressed.
- Specific aspects related to new inhaler technologies should be discussed and included in the guideline.

Pharmacokinetic studies (Step 2)

- The adequacy of using PK data to demonstrate similar efficacy and safety without the need for additional clinical data should be addressed.
- Given the limitations with imaging studies to conclude on therapeutic equivalence, the current recommendation should be reviewed.
- The current version states that pharmacokinetics should be studied in the intended patient population. This statement needs to be revised and specific information should be given regarding when healthy volunteers may be used for demonstrating therapeutic equivalence.
- Requirements for PK data on spacers and nebulisers should be reviewed.
- Variability in particle-size distribution between batches of the reference product or within a single batch of a reference product through their storage period can be significant. 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.

Pharmacodynamic / clinical studies (Step 3)

- The recommendations regarding study design, study population, endpoints, timing of measurement and acceptance criteria to demonstrate therapeutic equivalence should be standardised to the extent possible.

- Specific recommendations for fixed-dose combinations depending on the combination (e.g. LABA/LAMA combinations) should be given in the revised guideline.
- Recommendations are needed as to whether pharmacodynamic data obtained in healthy volunteers can be used to show therapeutic equivalence.
- Requirements for user studies on different inhaler devices and the required test panels (e.g. handling studies) should be addressed in more detail.

Data requirements in children and adolescents

- Data requirements for the paediatric population need to be discussed and re-considered in the revised guideline.

4. Recommendation

The Respiratory drafting group recommends revising the current guideline on orally inhaled products taking into account the issues identified above.

5. Proposed timetable

Released for consultation in March 2017, deadline for comments 30 June 2017, proposed date for release of draft guideline during 2018, deadline for comments 6 months later.

6. Resource requirements for preparation

The update of the guideline will involve representatives of Member States from the Respiratory drafting group and it should be discussed in approximately three of their meetings.

7. Impact assessment (anticipated)

The document is intended to provide guidance on how to establish therapeutic equivalence for orally inhaled products used in asthma and COPD. In addition, it will be useful to reach a common approach for the assessment of these products and scientific advice given by European regulatory authorities.

8. Interested parties

The pharmaceutical industry, European learned societies and scientific organisations (e.g. the European Respiratory Society). Consultation with other working parties or committees (e.g. QWP, PKWP and PDCO) will be initiated as appropriate.

9. References to literature, guidelines, etc.

Guideline on Pharmaceutical Quality of Inhalation and Nasal Products (EMEA/CHMP/QWP/49313/2005)

Clinical pharmacology and pharmacokinetics: question and answers (PKWP), question 3.3 and 3.4.

QWP Question & Answers on inhalation products.