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Committee for Medicinal Products for Human Use (CHMP)

Concept paper for the development of a guideline on the demonstration of therapeutic equivalence for nasal products

Draft agreed by Methodology Working Party, Quality Working Party and Rheumatology and Immunology Working Party	May 2024
Adopted by CHMP for release for consultation	15 July 2024
Start of public consultation	25 July 2024
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1. Introduction

The guideline on the pharmaceutical quality of inhalation and nasal medicinal products (EMEA/CHMP/QWP/49313/2005 Corr) (which is under revision) covers, as the title indicates, both orally inhaled products (OIPs) and nasal products. For OIPs there is a guideline, i.e., the guideline on the requirements for clinical documentation for OIPs including the requirements for demonstration of therapeutic equivalence (TE) 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 (CPMP/EWP/4151/00 Rev. 1) (also under revision) where all aspects related to TE are discussed. It is relevant to consider these documents together as *in vitro* data may be used for two purposes, both to characterise any new medicinal product (development, manufacture, control, stability) and as a strategy when showing TE in case of abridged applications, variations, and extensions. As the guideline CPMP/EWP/4151/00 Rev. 1 does not cover nasal products, it is deemed appropriate to publish a guideline specifically on TE for nasal medicinal products. The only reference made in the guideline on the pharmaceutical quality of inhalation and nasal medicinal products (EMEA/CHMP/QWP/49313/2005 Corr) is a paragraph stating that for nasal medicinal products claiming similarity to a reference medicinal product, data requirements for demonstrating TE may depend on the intended site of action of the active substance(s) i.e., whether the effect is locally or systemically mediated. The Note for guidance on the clinical requirements for locally applied, locally acting products containing known constituents (CPMP/EWP/239/95) and the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) are referred to. In addition, a list of quality attributes to be considered for i*n vitro* comparison is given.

The aim of this new guideline would be to detail the data requirements for demonstrating TE between nasal products containing the same active moiety(ies), as these are currently insufficiently covered in existing guidelines.

2. Problem statement

The intention of administrating an active substance into the nose could be to apply local treatment in the nose (such as e.g., products containing decongestants to be used in case of common cold or anti-inflammatory medication in case of allergic rhinitis). Another common use of nasal administration is as an alternative to injections to achieve rapid systemic exposure to an active substance following absorption through the nasal mucosa. The approach to take when demonstrating TE will differ dependent on whether the product is intended for local or systemic treatment.

In case of products intended for systemic therapy, the principles for comparable bioavailability/bioequivalence, i.e., pharmacokinetic (PK) endpoints measured in plasma, will apply and criteria for biowaivers could be set, if deemed appropriate. For locally active substances on the other hand, comparable bioavailability will only be relevant for safety unless there are PK endpoints serving as surrogate markers for local exposure in the nose. Currently, there is no consensus view or guidelines available detailing data requirements for TE for nasal products intended for local treatment.

3. Discussion (on the problem statement)

With the ongoing revision of the OIP guideline (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 (CPMP/EWP/4151/00 Rev. 1), the guideline presents a stepwise approach with a list of *in*

vitro criteria to be fulfilled and of additional PK studies to be conducted in case not all *in vitro* criteria are fulfilled. It is anticipated that a similar approach would be applicable for nasal products. Currently, abridged applications for locally active substances are supported by *in vitro* data on TE, sometimes, but not always, complemented by pharmacokinetic or clinical data. A number of *in vitro* parameters are to be considered:

- Qualitative and quantitative composition
- Actuation volume, single actuation content, or mass of single dose
- Droplet size distribution
- Mass of droplets smaller than 10 µm
- Particle size distribution and morphological form of active substance for suspensions
- Spray pattern / plume geometry
- Rheological properties (e.g., thixotropy, viscosity)
- Surface tension
- pH
- Density
- Osmolality
- Buffer capacity

Acknowledging that all these parameters might not be relevant for all formulations, and other parameters may be applicable depending on the finished medicinal product characteristics, it would still be of value to discuss these in more detail and set acceptance criteria for similarity. Thereby, data requirements on TE based on *in vitro* data only would be clearly set.

If TE cannot be concluded by means of *in vitro* data, *in vivo* data would be warranted unless the product is reformulated to fit the *in vitro* criteria. In case of systemically active substances, this would be data on comparable bioavailability/bioequivalence as outlined in the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98). For locally active substances there is currently no consensus on *in vivo* study designs and endpoints. Both pharmacokinetic (bioequivalence) and clinical data have been presented to support abridged applications, but it is uncertain what would be the preferred PK endpoints (if any) and to what extent sensitive clinical endpoints can be found. In the [OIP-guideline] it is recommended to avoid pharmacodynamic and clinical studies as it would be difficult to find designs allowing assay sensitivity to be shown at an acceptable level. This is likely the case also for locally active nasal products.

4. Recommendation

The Rheumatology and Immunological Working Party (RIWP) proposes to draft a guideline on demonstration of TE for nasal products.

5. Proposed timetable

The concept paper will be released for consultation for a three-month public consultation period. Proposed date for release Q3 2024.

6. Resource requirements for preparation

The development of the guideline will involve a drafting group who will develop the draft guideline for RIWP and proceed to develop a final version after the public consultation period. Consultation with other working parties or committees, e.g. Quality Working Party (QWP) and Methodology Working Party (MWP) will be initiated, as appropriate.

7. Impact assessment (anticipated)

A guideline would give recommendations to industry thereby facilitating product development and application processes. 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

Pharmaceutical industry, European learned societies and scientific organisations.

9. References to literature, guidelines, etc.

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

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 (CPMP/EWP/4151/00 Rev. 1

Note for Guidance on the clinical requirements for locally applied, locally acting products containing known constituents (CPMP/EWP/239/95)

Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)