European Medicines Agency

London, 19 March 2008
Doc. Ref. EMEA/CHMP/EWP/48501/2008
Appendix 1

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

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)

APPENDIX 1

DRAFT AGREED BY EFFICACY WORKING PARTY	March 2008
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	19 March 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 May 2008

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KEYWORDS	*CHMP, EMEA, Guideline, Drug Evaluation, Drug Approval, Orally inhaled products, Asthma, Chronic Obstructive Pulmonary Disease, Paediatric*

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EXECUTIVE SUMMARY

The guideline is a revision of the *CPMP Points to Consider on the Requirements for Clinical documentation for Orally Inhaled Products (OIP) CPMP/EWP/4151/00.* It clarifies the requirements for clinical documentation for abridged applications of orally inhaled formulations and variations/extensions to a marketing authorisation in respect of the demonstration of therapeutic equivalence between two inhaled products for use in the management and treatment of asthma and chronic obstructive pulmonary disease.

APPENDIX 1

Appendix 1 addresses the requirements for clinical documentation for abridged applications of orally inhaled formulations and variations/extensions to a marketing authorisation in respect of the demonstration of therapeutic equivalence between two inhaled products for use in the management and treatment of asthma in children

CHILDREN

The airway in the younger child differs from the airway in the adult and the amount of the dose of an inhaled drug reaching the lower airway in an infant and in a young child will differ from the amount which would reach the lower airway in an adult. Changes in development, maturation and growth of the lung from birth, through infancy and early childhood can affect absorption and clearance of drug from the lung with possible changes in respect of optimal dosing in this young age group and changes in both efficacy and systemic safety. The child also displays different breathing patterns and has differing tidal volumes, airway geometry, etc. compared with adults.

These differences between adults and children result in a number of scenarios where products shown to be equivalent in adults may not be equivalent in children or may not be appropriate for use in children in the way they would be used in adults. Such scenarios might include:

- the internal resistance of a dry powder inhaler device may be such that the device is more difficult for a child to use than an adult,
- the requirement that a child should always use a pressurised metered dose inhaler together with a specific spacing device, with and/or without a face mask, and the effect that such a device may have on the amount of the active moiety reaching the lung and the amount reaching the systemic circulation,
- differences which might exist between the test and the reference product which may be clinically irrelevant in adults may become clinically relevant in children, for example, a higher sensitivity in a child to adverse events,
- the need to develop a lower dose and/or a lower strength product for use in a child.

If such scenarios exist and an indication for use of a product in children less than 12 years of age is to be claimed assurance that both efficacy and safety in this young age group is appropriate is required. To this end, children with asthma and younger than 12 years **may** need to be studied in their own right.

The dose range for use in children must be defined and the **lowest limit** of the dose range for the reference product as authorised for use in children must be achievable with the new product if a claim of therapeutic equivalence is to be made.

In addition to the demonstration of equivalent efficacy assurance must be provided that the safety profile is unchanged (or improved on) compared with that of the reference medicinal product, particularly in respect of systemic safety (and this may need to be based on pharmacokinetic data and/or if necessary relevant pharmacodynamic data, for example, for inhaled corticosteroids investigation of the hypothalamic pituitary adrenocortical axis function and/or growth) at the top of the proposed dose range, such that the benefit/risk ratio remains unchanged or is improved compared with the reference product (see sections 4.3.2.3.1 and 4.3.2.3.2 of the Draft Guideline - Doc. Ref. CPMP/EWP/4151/00Rev.1).

Clinical Requirements

1. If the *in vitro* criteria for equivalence have **all** been fulfilled (see section 4.2.2 of the Draft Guideline) and therapeutic equivalence has been demonstrated indisputably in adults, **and** the inhalation device of the test product is pharmaceutically identical to that of the reference product which is approved in the intended paediatric population, clinical studies in children are generally **not** required.
2. If the *in vitro* criteria for equivalence have **all** been fulfilled (see section 4.2.2 of the Draft Guideline) and therapeutic equivalence has been demonstrated indisputably in adults, **but** the inhalation device of the test product is **not** pharmaceutically identical to that of the reference product **but** is approved in the intended paediatric population containing another active substance, clinical studies in children are generally **not** required.
3. If the *in vitro* criteria for equivalence have **all** been fulfilled (see section 4.2.2 of the Draft Guideline) and therapeutic equivalence has been demonstrated indisputably in adults, **but** the inhalation device of the test product is **not** pharmaceutically identical to that of the reference product and is **not** approved in the intended paediatric population, as an absolute minimum clinical requirement a handling study in this young age group will be required. This must be further supported by comparative *in vitro* data which must be provided to demonstrate that the test and reference product produce comparable fine particle performance through the flow rate and pressure drop range and air volume which are clinically applicable to children.
4. If **any** of the *in vitro* criteria for equivalence are **not** fulfilled (see section 4.2.2 of the Draft Guideline) or when equivalence cannot be demonstrated on the basis of the *in vitro* comparison, some clinical development of the product in children will be required unless an appropriate surrogate patient population can be justified. Demonstration of equivalent drug distribution combined with safety data (bioequivalence based on pharmacokinetic data and/or measurement of pharmacodynamic parameters, in as far as possible) generated following inhalation of the maximum recommended total daily dose regimen over an appropriate time period dependent on the active substance **might** be considered as sufficient demonstration of therapeutic equivalence.
5. If the findings of such studies do not permit the conclusion of therapeutic equivalence, therapeutic equivalence must be demonstrated then through appropriate clinical efficacy and safety studies. In these circumstances clinically relevant age-dependent endpoints must be evaluated (spirometric endpoints in the older child, 6 years and older, and clinical symptom scores in the younger child, 5 years and younger).

For detailed discussion on the clinical development of orally inhaled formulations in respect of the demonstration of therapeutic equivalence between two inhaled products for use in the management and treatment of asthma in children (see sections 4.3.1 and 4.3.2 of the Draft Guideline - Doc. Ref. CPMP/EWP/4151/00Rev.1). However non-inferiority margins cannot be extrapolated simply from those used in adults, they should be justified taking into account age and severity of disease.

If a pressurised metered dose inhaler is to be used in children it **must** be developed for use together with a specific appropriate spacing device(s) which will then be named in the SPC, the Patient Information Leaflet and possibly also on the product labelling. A pressurised metered dose inhaler should **always** be available for use with a specific named spacing device (see section 4.1.1.2 of the Draft Guideline - Doc. Ref. CPMP/EWP/4151/00Rev.1). The spacing device has to be appropriate for the age groups of intended use.

For adolescents aged between 12 and 17 years, interpolation from data generated in studies in adults may be possible if specific studies have also been carried out in children (less than 12 years). If not, a sufficient number of adolescents should be recruited to the adult studies such that the entire age range of intended use has been studied. Stratification for efficacy into a 12 to 17 years age group and 18 years and above is not necessarily required. However if specific studies have not been carried out in children authorisation in adolescents may require the generation of some clinical data in the adolescent, depending on the active substance. In these circumstances the demonstration of equivalent drug distribution combined with safety **may** be sufficient.