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POINTS TO CONSIDER ON THE REQUIREMENTS FOR CLINICAL DOCUMENTATION FOR ORALLY INHALED PRODUCTS (OIP)

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POINTS TO CONSIDER ON THE REQUIREMENTS FOR CLINICAL DOCUMENTATION FOR ORALLY INHALED PRODUCTS (OIP)

1 INTRODUCTION

This document is intended to complement the Note for Guidance for pharmaceutical documentation of inhalation products. Especially directed at the replacement of CFCs with HFAs the existing Note for Guidance "Replacement of Chlorofluorocarbons (CFCs) in Metered Dose Inhalation Products" (75/318/EEC - Council Regulation No. 594/91) describes how to conduct therapeutic equivalence studies for inhalative products in the field of asthma. In conjunction with the existing "Points to Consider on Clinical Investigation of Medicinal Products in the Treatment of Patients with COPD" (CPMP/EWP/562/98) and the "Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Asthma" (CPMP/EWP/2922/01), one can also apply the general rules for therapeutic equivalence studies to other inhalative forms of administration and to the therapeutic fields of studying patients with COPD, asthma or other diseases. Additional advice on the pharmaceutical and clinical development of orally inhaled products is given in the following Guidelines: "Clinical Requirements for Locally Applied, Locally Acting Products, Containing Known Constituents" (CPMP/EWP/239/95), "Guideline for PMS Studies for Metered Dose Inhalers with New Propellants" (CPMP/180/95), "Note for Guidance on Dry Powder Inhalers" (CPMP/QWP/158/96) and "Note for Guidance on Requirements for Pharmaceutical Documentation for Pressurised MDI Products" (CPMP/QWP/2845/00).

The data required are often linked to the in vitro performance data necessary for the proof of the product's quality. Also this document will address mainly specific issues of relevance to inhaler devices and cannot attempt to offer global guidance on all aspects of the clinical documentation for the whole product.

As an important additional information to clinical performance, efficacy and safety of the inhalation product administered via the technical system of an inhaler, the in vitro data, especially the flow-deposition characteristics of the product, will normally influence the information to be included in the SPC. This 'Points to consider' document is relevant for the following products:

- pressurised metered dose inhalers
- dry powder inhalers using a reservoir and metering mechanism
- dry powder inhalers using a predispensed dose
- non-pressurised, pump activated, liquid reservoir metered dose inhalers.

2 PHARMACEUTICAL PROPERTIES AND THE NEED FOR A CLINICAL PROGRAMME

2.1 New Active Substance

Regardless of the type of device, products with new active substances have to undergo the full clinical programme.

2.2 Well Known Active Substance

For abridged applications therapeutic equivalence to a licensed product must be substantiated. The only use of comparative in vitro data for this purpose is considered acceptable if the product satisfies all of the following criteria:

- the product contains the same active substance

- the physical state of the active substance is the same (dissolved or suspended)
- the delivered dose is the same
- the pharmaceutical dosage form is the same
- the inhalation device is identical in all parts which influence performance
- the qualitative and/or quantitative differences in excipients are known to have no influence on the deposition characteristics (e.g. Delivered Dose, FPD, MMAD, GSD) and on the inhalation behaviour of the patient (This should be justified for each excipient taking into account its amount.)

Identical in vitro performance has to be shown in order to prove comparable deposition characteristics and thus provide the basis for assuming that efficacy and safety profiles exhibit no clinically relevant differences. When testing with a standardised test procedure and apparatus comparable deposition characteristics does not mean comparable fine particle fraction in the smaller chambers representing the smaller airways alone.The upper performance representing the part of the drug which will be swallowed by the patient plays an important role as well. Adverse events resulting from systemic absorption derive from absorption from the lung as well as from gastro-intestinal absorption of swallowed drug substance.

For a complete description and to allow a comparison of the emitted clouds, assessments need to be made of the impaction of each stage, and throat in the same impactor (which must be multistage). Special emphasis needs to be placed on the <5 μm fraction, however.

In all other cases the normal method is the performance of therapeutic equivalence studies as described in the Note for Guidance "Replacement of Chlorofluorocarbons (CFCs) in Metered Dose Inhalation products" and the "Note for Guidance on Clinical Requirements for Locally Applied, Locally Acting Products, Containing Known Constituents" to compare the product with another licensed product containing the same active ingredient. A comparator should be the licensed innovator CFC product if still available, the CFC-free innovator product or the first authorisation of the CFC-free product of the same active substance. The choice of comparator should be justified.

In special cases – also described in the a.m. Guidelines - pharmacodynamic/pharmacokinetic studies may replace therapeutic equivalence studies. In these cases such studies should be conducted in patients, because deposition in the lung may show significant differences through the patients disease-related obstruction. Studies in volunteers alone are not acceptable.

When therapeutic equivalence to the licensed product cannot be demonstrated, a full phase III clinical programme has to be undertaken.

3 INHALATION DEVICES AND CLINICAL PROGRAMME

Propellant containing metered dose inhalers and dry powder inhalers show different flow deposition characteristics and their handling – and the resulting patient preference – is different. Therefore, the requirements for the clinical documentation regarding the device will be presented separately.

3.1 Metered Dose Inhalers (MDI)

MDI's contain different propellants (currently CFCs or HFAs, other propellants are under development). They may require hand-mouth co-ordination, but breath-operated devices also exist. Sometimes a spacer is additionally part of the application for marketing authorisation.

When a new propellant is introduced in an MDI, clinical aspects of safety have to be studied additionally to the toxicological and preclinical programme.

In this connection, local tolerability has to be regarded as well as mucociliary clearance and hyperreactivity including paradoxical bronchospasms.

3.1.1 Breath-Operated Inhalers (BOI)

A minimal inspiratory flow rate is required to trigger breath-operated inhalers. Whenever this minimal PIFR cannot be reached by the patient, the patient will not be able to use this inhaler. Therefore, the clinical documentation has to contain data about this triggering PIFR. It has to be discussed, which patient groups will normally be able to produce a sufficient PIFR to use this inhaler and which special groups may have problems (such as patients with severe asthma, patients suffering from an asthma attack, small children etc.). The relevant patient population must be adequately defined to allow the prescriber to ensure that the product is only used by suitable patient groups.

The reference product for a BOI can be the equivalent MDI. There are particular circumstances in which equivalence between BOI and MDI can be claimed without a full clinical programme. This may be possible in a situation where:

- the actuator mouthpiece designs are identical
- the flow paths of the aerosol cloud are the same
- all target patient populations can generate the same flow rates through the MDI and BOI
- all patients can trigger the inhaler adequately
- the in-vitro characteristics defined in section 2.2 are equivalent
- there is no other reason to expect differences in lung deposition.

In a situation where in-vitro deposition characteristics are identical but there is doubt about another parameter, it may be possible to prove equivalence using a single dose pharmacodynamic/ pharmacokinetic study.

In cases where inhalers can be breath-operated as well as hand-operated, patients need an explanation in the leaflet as to how to recognise an insufficient breath-operated inhalation and how to switch to a hand-operated inhalation procedure. The two modes of action should be compared using the parameters outlined above to determine whether there is a need for clinical data to support each method of operation.

3.1.2. Spacers

There are specific expectations related to the use of spacers and additionally there may be special claims by the applicant. Whenever all clinical studies have been conducted only with the product plus spacer, the product can be licensed only for the use with spacer as data about the product's performance itself do not exist. This has to be stated clearly in the SPC.

If the product can be administered with and without spacer, the use of the product alone as well as the use of the product with spacer must be supported by clinical data and additionally by comparative deposition in vitro and in vivo data.

Any claim exceeding instructions for use and handling (no breath-hand co-ordination is needed with spacer), e.g. reduction in the amount of large particles, additionally has to be supported by in vitro data.

A differentiation between integral spacers which are part of the medicinal product and external spacers which are medical devices is necessary.

3.2 Dry Powder Inhalers (DPI)

In comparison with MDI's, DPI's often show a much higher flow dependency in their deposition characteristics. Therefore, critical evaluation of flow rate dependency is necessary and clinical studies should be performed in relevant patient groups and severity stages to show that the product is effective and can be used safely. The clinical documentation also has to present sufficient data to describe the flow deposition characteristics of the products within the range of clinically relevant flow limits. In addition to the clinical data, in vitro and in vivo deposition data are necessary. Section 3.1.1. is also valid for DPI's with a trigger mechanism.

A high flow dependency in a DPI acting as reference product in a clinical study may also produce problems because the conclusion "therapeutic equivalence" does not say anything about the question, to which deposition rate (depending on the average flow the patients have been able to produce) this equivalence is stated.

Marketing authorisation cannot be granted for inhalers with a high flow dependency where deposition rate values with high flow rates reach many times the amount of deposition rate values with low flow rates.

For all DPI's the patient population which will be able to use the inhaler should be defined.

3.3 Relationship Between Inhaled Dose and Deposition Characteristics

In cases where different dose strengths of the same product containing a well-known active substance are sought, it can be sufficient to state the therapeutic equivalence clinically in vivo with one of those dose strengths. Thereafter it is necessary to give proof of a linear dose deposition relationship in vitro for each of the other dose strengths performed with a multistage impactor. Sometimes the deposition worsens with higher nominal doses per inhalation. In cases where data for different dose strengths do not show linearity sufficiently, additional clinical data have to be provided. Marketing authorisation cannot be granted when deposition varies so much between dosage strengths that dose titration is impractical or unsafe.

Asthma is not a static disease. It worsens and becomes better depending on many intrinsic and extrinsic factors. So during therapy patients often need a dose adjustment and for reasons of compliance often switch between different dose strengths of a product. A patient inhaling twice a day four times from a special inhaler and therefore getting another product with fourfold dose strength so that he has to inhale only once twice a day (and vice versa) must be able to rely on the same efficacy and safety of that other dose strength when the same nominal amount of active substance is applied.

4 THERAPEUTIC EQUIVALENCE STUDIES

When testing for the bioequivalence of inhaled anti-asthmatic drugs, such as new formulations, new inhalation devices or new propellants, special problems may arise that make conventional bioequivalence studies inappropriate. In these circumstances therapeutic equivalence must be shown.

Pharmacodynamic studies may be sufficient to support a claim of equivalence of two inhaled bronchodilators. For other classes of anti-asthmatic drugs clinical efficacy and safety studies are generally required to show therapeutic equivalence. Comparative studies of in vitro inhaler performance, in vivo lung deposition and pharmacokinetics have yet to be validated as surrogates of the safety and efficacy of inhaled anti-asthmatic agents. Pharmacokinetic data are useful to assess systemic safety.

An adequate run-in period to demonstrate stability of baseline disease severity should be included. Studies comparing inhaled glucocorticosteroids should show prior to randomisation that baseline

dosage was the minimum required consistent with asthma step-down guidelines. Use of steroid-naïve patients is preferred whenever possible.

Clinical efficacy and safety studies in appropriate patients should investigate a range of doses including the top recommended dose for safety and the lowest dose to show the minimally effective dose. The primary efficacy variable(s) should be identified a priori. The magnitude and duration of effects should be documented over an appropriate period of time. The duration of the therapeutic equivalence studies should be appropriate for the active drug. In the case of inhaled glucocorticosteroids a double-blind, randomised, parallel-group design of a minimum duration of 6-8 weeks is recommended to exclude any loss of asthma control versus the licensed comparator.

In a trial designed to show therapeutic equivalence the clinical significance of the chosen difference of no clinical importance (Δ) should be discussed.

Changes to inhaled excipients or to the pulmonary deposition may affect clinical safety. Appropriate safety data, for a minimum observation period of 3 months, should be collected.

For more detailed information regarding the bioequivalence issue of orally inhaled products the following guidances should be considered:

- "Replacement of Chlorofluorocarbons (CFCs) in Metered Dose Inhalation Products" (75/318/EEC - Council Regulation No. 594/91)
- "Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Asthma" (CPMP/EWP/2922/01)
- "Clinical Requirements for Locally Applied, Locally Acting Products, Containing Known Constituents" (CPMP/EWP/239/95)

5 CLINICAL TRIALS AND CHANGE OF PHARMACEUTICAL SPECIFICATIONS

It has to be borne in mind that several pharmaceutical specifications (e.g. fine particle dose) have to be adjusted to the pharmaceutical results of the batches of the product used in the clinical studies.

When therapeutic equivalence or an acceptable estimation of efficacy and safety are stated as a result of a clinical study with a product showing certain specifications, less favourable specifications cannot be set afterwards without giving up the possibility of drawing conclusions from the clinical studies.