The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

London, 24 June 1998
CPMP/QWP/158/96

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

NOTE FOR GUIDANCE ON DRY POWDER INHALERS

DISCUSSION IN THE QUALITY WORKING PARTY (QWP)	Feb., July, Oct. 1996 Jan., June, Oct. 1997
TRANSMISSION TO THE CPMP	October 1997
TRANSMISSION TO INTERESTED PARTIES	October 1997
DEADLINE FOR COMMENTS	April 1998
ADOPTION BY CPMP	June 1998
DATE FOR COMING INTO OPERATION	December 1998

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DRY POWDER INHALERS

1. INTRODUCTION

Although Dry Powder Inhaler systems have been marketed for a number of years, the need to remove CFCs from formulations, particularly Metered Dose Inhalers (MDIs) has prompted the increased development of Dry Powder Inhalers (DPIs) as an alternative to reformulations of CFC free MDIs.

Tere are two basic differences between the DPI and MDI systems:

i) DPIs are liquid-free systems. This may give rise to problems of particle cohesion and compaction not seen in MDIs and moisture may have a significant influence on these properties:

ii) Current DPIs often rely on the patients inspiratory effort to inhale the required dose of product and to deaggregate the particles in the inhaled dose.

There are likely to be many different types of device developed by the pharmaceutical industry, with different internal component configurations, different means of presenting the powder mass, measuring a dose and causing particle aerosolisation

In practice two different types of DPI can be distinguished, predispensed (single dose) systems which use capsules or blisters to contain one dose and Reservoir systems which remove a dose by some means from a powder mass equivalent to many doses and present this to the patient.

This guide identifies some of the important issues for consideration during the development of DPIs. It is not intended to be comprehensive as aspects of a general nature which apply to all applications are not included. The guideline indicates where the information should be presented in the dossier of a Marketing Authorisation Application.

This guideline primarily considers quality aspects of DPI development. For guidance on clinical testing of these products, reference should be made to the guidelines Clinical Requirements for Locally Applied Locally Acting Products Containing Known Constituents and Replacement of CFCs in Metered Dose Inhalation Products.

1.1 Expression Of Dose

It is evident that because of the differing efficiencies of different devices and the characteristics of the formulation they contain, different devices containing the same active ingredient can deliver the same effective ("fine particle") dose from different metered amounts of active ingredient.

This will create significant problems both to prescriber and patient as different labelled (metered) doses could be therapeutically equivalent.

This presents a sound argument for abandoning the usual concept of metered dose and developing instead a "fine particle" dose based upon the mass of active potentially capable of reaching the lung as indicated in a suitable multistage impactor or impinger test.

Some progress has been made in the new European Pharmacopoeia Inhalanda monograph which defines a fine particle dose as that fraction of the delivered dose which is less than 5µm and also gives a method for its determination.

However, until more experience is gained with this expression of "dose", manufacturers may wish to reduce confusion by developing products for which therapeutic equivalence is established through the same delivered or metered dose. Where manufacturers have adopted an alternative approach, the SPC should specify that the product is not inter-changeable with any other.

It should be borne in mind that for the moment therapeutic equivalence between different devices and/or different metered or delivered doses is based on in vivo studies.

2. Pt II A - COMPOSITION OF THE MEDICINAL PRODUCT/DEVELOPMENT PHARMACEUTICS

Data regarding air flow resistance of the device, uniformity of dose delivered by the device and particle size assessment of the delivered powder should be presented, the following should be noted:

2.1 Dose Uniformity

'Uniformity of Delivered Dose' of the European Pharmacopoeia.

This relies on extracting powder from the DPI and retaining it in the specified apparatus. Compliance with this test should be demonstrated.

It should be noted that there is no requirement for the mean in this test to meet any specification with respect to nominal (labelled) content per actuation. It should be possible for the applicant to attain a mean in this test of ±20% (or tighter) from the nominal content per actuation, using the current Ph. Eur test procedure.

In any event, the specification must be based on the performance of the batches used clinically taking into account the tolerances of the devices and variability of the batches used in the clinical work.

2.2 Air Flow Resistance

It is characteristic of DPIs, that their design influences the air flow resistance of the device and the airflow rate achieved by the patient. This has a number of implications.

2.2.1 The DPI can only be used by a patient capable of inhaling adequately through it.

2.2.2 The dose determined in vitro may be dependent upon the airflow rate chosen to test the system.

2.2.3 The particle size distribution of the delivered dose evaluated in vitro will also depend upon the airflow rate chosen to test the system.

The methods for Uniformity of Delivered Dose and Aerodynamic Assessment of Fine Particles of the European Pharmacopoeia are conducted at a flow rate relevant to the inhaler being tested determined using a fixed pressure drop of 4 kPa across the inhaler (with a maximum flow rate of 100 $l.min^{-1}$) to account for these design differences.

This is important not only for multidose inhalers but also for single dose systems.

2.3 Aerodynamic Assessment Of Fine Particles

Applicants should present data from a multistage impactor determined using the method of the European Pharmacopoeia at the relevant flow rate. For release purposes a Finished Product Specification based on a suitable two stage system may be acceptable if this has been validated against the performance of the DPI in a multistage impactor.

Drug mass deposition data from each stage should be presented.

The drug mass on each stage and the cumulative mass undersize a given stage should be determined rather than the % emitted dose (or other derived parameter) as these can hide variations in dose delivered.

The limits applied should be based on the batches used clinically taking into account the tolerances of the devices and the variability of the batches used in the clinical work.

It is also usual to present data graphically e.g. as cumulative % found less than a stated diameter versus diameter. From this a MMAD and GSD may be calculated.

2.4 The Formulation

2.4.1 Formulations are generally simple in that a small number of components are included. In some products the only component is the active ingredient, but it is expected that excipients, particularly lactose, will be used in the majority of systems.

2.4.2 In order that the powders can be mixed effectively to form a suitable mass and be readily deaggregated by the patient's inspiratory effort, particle characteristics such as size, shape, rugosity and charge are critical.

Although all of these parameters are capable of quantification it is expected that only particle size and size distribution will be monitored routinely.

It is essential therefore that the applicant has a suitable multipoint size specification for the active ingredient(s) and excipient(s) or where appropriate, for granules of excipient and/or active when these are used rather than a powder mix. These specifications may be determined by methods other than impaction e.g. laser diffraction.

Specification limits should be supported by data from studies demonstrating the suitability of the extremes of the specification - in vitro data (multistage impactor or impinger) should suffice for this purpose.

2.4.3 To try and standardise the shape/rugosity parameters it is essential that the grade of each excipient is specified. The applicant should either

i) demonstrate the suitability of the material from different sources including different batches from each source.

or

ii) limit the source of each active/excipient to one supplier and demonstrate the suitability of different batches.

Providing that paragraphs (i) or (ii) are complied with, no specification for shape/rugosity is required.

It should be assessed whether flow properties of the excipients and powder mix or other physical characteristics affect the functionality of the product.

2.4.4 Because reservoir multidose DPIs often rely on the formulation of a cohesive blend formed by particle/particle interactions, the vibrational stability of mixtures formed from each source material should be demonstrated to simulate in-use vibrations during transport and use.

Vibrational stability assessment following subjection of reservoir multidose DPIs to conditions of elevated temperature and humidity is useful in assessing potential problems in-use.

Batch analyses data (including composition and particle size distribution of components) from the batches used in clinical trials, should be presented to justify the

specifications give in Pt II C for all types of dry powder inhalers. If the formulation used in clinical trials is different to that proposed for marketing sufficient comparative data including component size distributions, dose uniformity and fine particle assessment should be presented.

2.4.5 Particle and device surface charge, development of charges during filling processes and in-use streaming of particles themselves are problems to be considered in order to better determine the components of a formulation and the materials of construction of the device. Another practical problem is also that prototype devices may be of different materials of construction to the marketed product. Differences in charge because of particle interactions with these different materials may lead to differences in the size distribution of the delivered dose or the quantity of powder delivered per actuation. This may have implications in the clinical studies presented with the dossier and parameters such as dose uniformity and fine particle assessment must be presented for prototype and final devices if these are used in the development programme. These should be evaluated at the air flow rate relevant to each device.

As the development of surface charge is dependant upon the ambient relative humidity, the assessment of dose uniformity and fine particle assessment should be undertaken at different relative humidities during the development programme.

2.5 Through Life Performance

Dose delivery and particle size characteristics should be maintained over the shelf life of the product and during the period it is being used.

In reservoir devices, an overage of powder mass will probably be included to ensure adequate performance over the in-use period. Performance over the nominal content of the inhaler as indicated by the dosage indicator should be presented.

However for reservoir devices, data should also be presented to illustrate performance to exhaustion as it may determine the strength of any discard warning needed in the Patient Information Leaflet and on the carton.

3. Pt II B - METHOD OF PREPARATION

Results of process validation studies regarding the filling process should be submitted. If the formulation is a mixture of components, the mixing process should be fully validated.

Parameters for any physical tests proposed should be similarly derived.

4. Pt II C1/2 - CONTROL OF STARTING MATERIALS

Suitable multipoint particle size specification and test methods for the active substance and excipient should be prepared in line with those in the batches used in clinical trials. Batch analyses data should be presented.

5. Pt II C3 - CONTROL OF PACKAGING MATERIALS

The specification for the inhaler should be presented to include details of dimensions and materials of construction. Where the device requires accreditation with a 'CE' mark, evidence of this accreditation should be presented although all devices have to fulfil the 'Essential Requirements' as outlined in Annex 1 of Council Directive 93/42 EEC.

5.1 The Device

For reservoir systems each unit should have the following two safety features:

i) a counter or other fill indicator to give the patient some indication of when the number of actuations stated on the label has been delivered.

ii) a system to prevent inadvertent multiple dosing because of multiple actuations of the dose measuring device before use by the patient.

Where this safety feature is not present i.e. the device can be actuated repeatedly, the applicant should demonstrate that this does not lead to multiple doses being inhaled by the patient.

6. Pt II E - CONTROL TESTS ON FINISHED PRODUCT

The finished product specification should include the following parameters:

6.1 Dose uniformity:

for reservoir and multidose (predispensed) inhalers a content uniformity test which assesses inter and intra inhaler dose uniformity should be defined based on the intra inhaler test and specification described in the European Pharmacopoeia.

6.2 Number of deliveries from the container.

6.3 Aerodynamic assessment of fine particles as discussed above.

6.4 Microbial purity (Ph. Eur. 3rd Ed (5.1.4))

7. Pt II F2

7.1 Stability

7.1.1 Standard stability parameters such as active ingredient assay and related substances will be included.

7.1.2 The main stress which will affect this type of product is moisture which may affect the aerodynamic particle size, dose and dose uniformity. Even with single dose preparations moisture ingress may be a problem and the effect of moisture stress on storage should be monitored. For single dose capsule preparations moisture uptake by the shell may affect capsule opening or release of the capsule contents.

For multidose inhalers, the inhaler configuration may demand that information on drug delivery performance be provided for DPIs stored without a removable/replaceable cap in place to see how sensitive the product is to moisture when the cap is mislaid.

Stability studies on the finished product should be carried out at 25°C/60% RH and 40°C/75% RH in accordance with the ICH Guideline for Stability Testing of New Drug Substances and Products. If at expiry, the product complies with the end of shelf life specification after storage at these conditions an additional instruction for protection from moisture is not necessary.

If the product is packed in a paper, foil or plastic overwrap, it is essential to test it without this in place but this can be of limited duration (3-6 months) to simulate the in-use situation. If the results so indicate, it may be necessary to stipulate protection from moisture for the product after removal of any overwrap.

GLOSSARY

CFC

Chloro fluoro carbon (propellant for Metered Dose Inhalers)

DPI

Dry Powder Inhaler

Delivered dose

The amount of active ingredient contained in the mass of powder delivered to the patient. This represents the metered dose minus any powder retained in the device.

GSD

$$\frac{\text{diam } 84.13\%}{\text{diam } 15.87\%}^{1/2}$$

from the plot of cumulative percent undersize versus size of a log normal distribution.

Metered dose

The amount of active ingredient contained in the mass of powder volumetrically dispensed from a powder bed contained in a device by a suitable metering mechanism.

MDI

Metered Dose Inhaler

MMAD

Mass Median Aerodynamic Diameter

[The aerodynamic diameter is the diameter of a sphere of unit density having the same terminal settling velocity as the particle. The median diameter is that dimension which divides the size distribution into two equal parts by weight.]

Predispensed dose

Refers to DPIs which contain individual doses of active ingredient held as discrete units within the device.

The fine particle dose (respirable dose)

The mass of active ingredient capable of being inhaled into the lung. This represents the delivered dose minus any powder deposited in the oropharynx and is generally regarded as being the mass of active ingredient consisting of particles below 5µm in diameter.

SPC

The Summary of Product Characteristics presented in accordance with article 4a of Directive 65/65 EEC.