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

London, March 2002

CPMP/QWP/2845/00

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

NOTE FOR GUIDANCE ON REQUIREMENTS FOR PHARMACEUTICAL DOCUMENTATION FOR PRESSURISED METERED DOSE INHALATION PRODUCTS

DISCUSSION IN THE QUALITY WORKING PARTY (QWP)	June and October 2000
TRANSMISSION TO THE CPMP	November 2000
RELEASE FOR CONSULTATION	November 2000
DEADLINE FOR COMMENTS	May 2001
DISCUSSION IN THE QUALITY WORKING PARTY (QWP)	June, October 2001, Jan 2002
TRANSMISSION TO CPMP	March 2002
ADOPTION BY CPMP	March 2002
DATE FOR COMING INTO OPERATION	1 October 2002

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NOTE FOR GUIDANCE ON REQUIREMENTS FOR PHARMACEUTICAL DOCUMENTATION FOR PRESSURISED METERED DOSE INHALATION PRODUCTS

1. INTRODUCTION

Initial guidance for industry was published in 1993 with the guideline 'Replacement of Chlorofluorocarbons in Metered Dose Inhalation Products' (111/5378/93).

This guideline was developed primarily for metered dose inhalation products (MDIs), which were being reformulated to replace chlorofluorocarbons (CFCs) by non-CFCs and may still afford additional guidance for these products. The quality aspects of the CFC replacement guideline are now separated from the safety and efficacy aspects in order to make the requirements applicable to all pressurised metered dose inhalers (pMDIs). The safety and efficacy aspects in the CFC replacement guideline remain valid until revision. Although guidance on the pharmaceutical documentation is now presented separately from that on clinical testing, it is not intended to imply that there is no relationship between the two and the importance of linking in vitro performance data with the clinical data package cannot be overemphasised.

The guideline in general addresses specific issues of relevance to pMDIs and does not attempt to offer global guidance on all aspects of product development and testing. Reference must be made to other CPMP guidelines where relevant e.g. in areas of pharmaceutical development, stability testing etc and to the Ph.Eur monograph 'Inhalanda'.

2. EXPRESSION OF DOSE/CONTENT PER ACTUATION

The content per actuation, which is reflected in the labelled 'strength' of the preparation, can be expressed either ex valve (metered) or ex actuator (delivered). Within the EU there is no common consensus for this expression especially with historical products. In order that consistency is achieved in the future, all products containing new chemical entities and products containing known active ingredients used in inhalation products for the first time should be labelled with the delivered dose but for existing products current practice in each Member State should be followed.

3 SEC 3.2.S DRUG SUBSTANCE DATA

For suspension formulations, a suitable multipoint particle size specification should be developed for the active ingredient justified primarily by reference to batches used clinically.

Changes in the state of solvation (or desolvation) of the active ingredient should be investigated and the physico-chemical problems which arise if such change is observed (e.g. crystal growth on storage) should be addressed.

4. SEC 3.2.P.2 PHARMACEUTICAL DEVELOPMENT

The 'Pharmaceutical Development' section should contain details of the product development history to explain the process of formulation and device optimisation. Sufficient data should be provided to support the specifications proposed or to give adequate assurance that those performance characteristics, which may not be routinely tested e.g. priming and testing to exhaustion, have been adequately investigated. Similar performance specifications will be required for both solution and suspension formulations.

Support for the specification may also be included in Sec 3.2 P511E.

4.1 Moisture Content

The effect of moisture content on product performance on stability should be evaluated. A specification will only be required if the product has a demonstrated sensitivity to moisture.

4.2 Delivered Dose

The uniformity of the delivered dose should be evaluated by the test described in the European Pharmacopoeia appropriate for oral inhalation products. If the labelled strength of the product is expressed as delivered dose (ex actuator), the average value should be within ±15% of the labelled dose. For products labelled with metered dose, the same limits should be applied if the metered dose is evaluated by direct measurement. If, however limits are derived from the delivered dose taking into account the retention in the mouthpiece wider limits may be acceptable.

Retention in the mouthpiece should be evaluated and consistent with the delivered dose.

The content uniformity of the delivered dose between canisters of a batch must be sufficiently guaranteed. In this respect the homogeneity of the suspension/solution during the filling process and the fill weight/volume are considered as important parameters influencing the content of uniformity. The production process should be validated regarding these parameters, in connection with the uniformity of the delivered dose.

A test should be performed to evaluate the uniformity of delivered dose between an appropriate number of canisters in a typical production batch.

The dose uniformity has to be assessed from the last nominal shot to exhaustion using three

canisters from at least two different batches.

4.3 Fine Particle Dose

The particle/droplet size distribution of the active substance in the emitted aerosol cloud should be evaluated using a suitable multistage impactor/impinger and method of calculation of fine particle dose as described in the European Pharmacopoeia.

The number of actuations used in this test should be minimized as close to the patient dose as possible taking analytical sensitivity and delivered dose uniformity into consideration. If applicable, containers need to be primed before testing as directed in the PIL.

Determination should be undertaken at the start and end of nominal content and at intervals to the point of exhaustion of the container. These latter data are required even if the actuator has a dose counter.

Drug mass deposition data from each stage should be presented, including the mass of active substance in the induction port, mouthpiece adaptor and, where used, the pre-separator. It is also helpful to present these data graphically as amount deposited per impinger/impactor stage.

From the data derived from the batches used clinically, it is necessary to define a lower and an upper limit for the fine particle dose (FPD) for release purposes. This specification must be maintained throughout the life of the product, unless an alternative shelf life specification has been validated clinically. In determining routine compliance with this specification it will only be necessary to evaluate data from the beginning of the nominal content of the containers tested providing that sufficient data has been generated in development and on stability to give confidence in the FPD of the product through the volume of the container over the shelf life of the product. Although it is recognised that a different parameter may need to be measured for routine release testing, a single stage impactor/impinger can be used following cross-validation to the apparatus used in development studies and with reference to the batches used in the clinical studies.

4.4 Priming

The need for priming actuations

- Before first use of the canisters
- After a time period typically allowed to elapse between doses as stated on the label
- After an extended period of non-use (3-5 days, as justified)

should be addressed to ensure that the uniformity of content requirements are met in normal use.

The priming results should be obtained with at least three canisters of one batch.

Information on when and how to prime should be included in the Summary of Product Characteristics (SPC) and the Patient Information Leaflet.

4.5 Extractables

Data should be provided demonstrating the extent of extraction of components into the formulation from the container and valve monitored to the point at which the extraction reaches equilibrium or to the end of the proposed shelf life of the product whichever is earlier.

Where possible extracted and particularly leachable compounds should be identified and in all cases the toxicological implications of the leachable profile should be discussed in Module 4.

Information should also be provided on any processes used for the pre-extraction of components prior to use either by the component manufacturer or applicant. Such processes should be shown to produce the required end product consistently.

The quality specification for the components should ensure that in routine use the extractable profile is consistent with that determined during development and on stability.

4.6 Use of Spacers

When a spacer is recommended for a certain product, its use should be validated and relevant information given in the Summary of Product Characteristics (SPC).

Comparative *in vitro* data for the fine particle dose should be generated on the pMDI, with and without the spacer, to demonstrate the physical compatibility of the spacer and pMDI. In addition, the use of the spacer should be adequately supported by the appropriate use of the spacer in the clinical programme.

Clinical claims associated with the use of the spacer will need to be justified in clinical studies.

(See also Points to Consider on the Requirements for Clinical Documentation for Metered Dose Inhalers)

4.7 Breath Actuated Devices

Data should also be provided to demonstrate that all target patient groups are capable of triggering the breath-actuated device. This could be evaluated as part of the clinical programme during patient handling studies. Furthermore, the triggering mechanism should be well characterised as part of the device development programme.

4.8 In-use performance

The performance of the product has to be investigated under simulated conditions of normal use by patients in accordance with the directions in the SPC/PIL. The effect of low and high temperatures on the performance of the inhaler should be assessed.

4.9 Cleaning Procedure

The cleaning procedure for the spacer and MDI should be clearly described. Data must be submitted providing evidence of no change in the aerodynamic particle size distribution due to the cleaning procedure.

5 SEC 3.2P.3.3 DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS

Process Validation

Manufacture of pMDIs is considered to be a non-standard method of manufacture (see CPMP Note for Guidance on Process Validation). Data demonstrating the validity of the process should be submitted in the marketing authorisation dossier. Data should be provided on three consecutive batches at production scale prior to approval. However, data on 1 or 2 production scale batches may suffice where these are supported by pilot scale batches and by a history of consistent manufacture of products by an essentially equivalent process. In the latter case, post-approval, additional process validation data should be generated on 3 production batches.

The homogeneity of the suspension/solution during the filling process and the fill weight/volume must be validated. Results from the beginning, middle and end of the filling procedure should be provided as a minimum. The fill weight/volume should be included in the in-process controls.

6 SEC 3.2.P.4 CONTROL OF EXCIPIENTS

When excipients, even if well known are used in inhalation products for the first time, the issue of toxicity, particularly over the long term, should be addressed. The purity specification proposed should be justified by reference to batches used in preclinical tests.

7 SEC 3.2.P.5 CONTROL OF DRUG PRODUCT

In addition to the normal quality characteristics to be controlled in the Finished Product tests of identity, assay and related substances, the following should be included:

7.1 Moisture Content *(if relevant)*

7.2 Delivered Dose and Uniformity of Delivered Dose

The product should comply with the Ph.Eur. requirements and the specification described in 4.2 above. Uniformity of solution formulations may be evaluated using weight determinations.

7.3 Fine Particle Dose

7.4 Leak Rate

7.5 Number of deliveries per inhaler

Microbial purity

7.6 (Foreign) Particulate Matter

Where a separate shelf life specification is requested for any parameter, this should be clearly stated and justification provided.

Periodic testing for specific tests may be considered where sufficient data are presented to demonstrate that the batches would meet the requirements for those tests, if tested.

8. SEC 3.2.P.7 CONTAINER CLOSURE SYSTEM

The specification for each component of the inhaler critical to the performance or manufacture of the product should be presented to include details of the supplier, dimensions, dimensional tolerances and materials of construction. Clear diagrams should be provided and compliance of batches submitted in the Marketing Authorisation Application with the specifications should be demonstrated.

Specifications for all components in contact with the formulation should ensure compliance with the specification for limits of leachable components including, where necessary, a pre-extraction phase. Where the leachable profile does not present a safety concern, compliance

with the specification can be demonstrated by testing batches periodically.

If the aerosol canisters have an internal coating, specifications for this should be given. The integrity of the inner surface should be demonstrated in stability testing protocols.

9 SEC 3.2.P.8 STABILITY

Stability data should be generated in accordance with the relevant guidelines. For the purposes of QWP/556/96 relating to stability testing of existing active substances and products, pMDIs should be regarded as critical products in relation to selection of batches and minimum duration of studies.

In addition to standard testing conditions, temperature cycling should also be performed for a minimum period of six weeks, the conditions used should be justified by the applicant. However, if sufficient data are generated with the marketed product during development, this requirement may be omitted from the stability protocol.

In designing the studies, product should be stored in the valve up and valve down orientations, appropriate bracketing and matrix designs will be acceptable. Data should be presented separately for each orientation.

The parameters investigated during the stability trials should include the specification tests, with the exception of the identity test, in addition to usual attributes such as related substances, leachable moisture and microbial purity

If the pMDI is packed in a stability protective 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. It is essential when testing the exposed products to investigate sustained product performance through to container exhaustion at intervals over this testing period.

10. SUMMARY OF PRODUCT CHARACTERISTICS

Section 2: Qualitative and Quantitative Composition

It should be clearly stated if the labelled claim is expressed as ‘metered dose’ (ex valve) or ‘delivered dose’ (ex actuator).

Section 4.2: Posology and Method of Administration

If applicable, the use of any specific spacer must be mentioned.

In this section the use of the MDI and/or spacer have to be clearly indicated. Directions should be stated regarding the need for priming.

Section 6.4: Special Precautions for Storage

The following statement should be included: The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not pierce the canister.

Cleaning

If applicable, a detailed description of the cleaning instructions for the spacer and/or actuator has to be given.