European Medicines Agency
Inspections

London, 16 February 2005

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)

GUIDELINE ON THE PHARMACEUTICAL QUALITY OF INHALATION
AND NASAL PRODUCTS

<table>
<thead>
<tr>
<th>DISCUSSION IN THE QWP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION</td>
<td>19 January 2005</td>
</tr>
<tr>
<td>END OF CONSULTATION (DEADLINE FOR COMMENTS)</td>
<td>30 July 2005</td>
</tr>
</tbody>
</table>

Note: This Guideline has been prepared in collaboration with Health Canada and represents a harmonised Guideline. It should be noted that Annex III on Devices, Spacers and Holding Chambers is EU specific only.

Comments should be provided to qwp@emea.eu.int by 30 July 2005, Fax +44 20 7418 8595
GUIDELINE ON THE PHARMACEUTICAL QUALITY OF INHALATION AND NASAL PRODUCTS

TABLE OF CONTENTS

1. INTRODUCTION

2. DRUG SUBSTANCE SPECIFICATION

3. DRUG PRODUCT PHARMACEUTICAL DEVELOPMENT
   3.1 Inhalation Products
   3.2 Nasal Products

4. DRUG PRODUCT MANUFACTURE

5. EXCIPIENTS
   5.1 Pharmacopoeial Excipients
   5.2 Non-pharmacopoeial Excipients

6. DRUG PRODUCT SPECIFICATION(S)
   6.1 Inhalation Products
   6.2 Nasal Products

7. DRUG PRODUCT CONTAINER CLOSURE SYSTEM

8. DRUG PRODUCT STABILITY

9. GLOSSARY

REGION-SPECIFIC APPENDICES
   I Generic Products
   II Information for Consumers and Health Care Professionals
   III Devices, Spacers and Holding Chambers (European Union only)
1. INTRODUCTION

This guidance document applies to human medicinal products intended for delivery of the drug substance into the lungs, or to the nasal mucosa, with the purpose of evoking a local or systemic effect. It includes current technologies for administration of the drug substance to the lungs, such as pressurised metered dose inhalers, dry powder inhalers, products for nebulisation, and metered dose nebulisers, as well as pressurised metered dose nasal sprays, nasal powders, and nasal liquids for nasal delivery. Nasal ointments, creams and gels are excluded.

This document outlines expected quality aspects of products to be marketed, but the general principles described here should also be considered for products used in clinical trials. It is not expected that all described testing would be conducted on all clinical trial batches. However, extensive characterisation of the drug substance and drug product batches used in pivotal clinical trials is necessary to qualify the product proposed for marketing.

This document does not outline expected quality aspects related to changes in existing inhalation and nasal products. However, the general principles apply.

Only quality aspects specific to inhalation and nasal products are discussed here. Additional quality aspects (e.g., impurities, process validation, stability testing) are described in other guidance documents.

Detailed guidance on pharmaceutical development study design (e.g., priming studies) and the analytical procedures used primarily for inhalation and nasal products (e.g., cascade impactor analysis) has not been provided. Some of this information may be found in other publications (e.g., United States Pharmacopeia, European Pharmacopoeia). It is also recognised that the wide diversity of inhalation and nasal products with respect to formulation and device characteristics necessitates some flexibility in testing methodology.

2. DRUG SUBSTANCE SPECIFICATION

For all inhalation and nasal products containing a drug substance that is not in solution at any time during drug product manufacture, storage, or use, the drug substance specification should include a particle size test and limits. A validated, multi-point particle sizing method (e.g., laser diffraction) should be employed.

Acceptance criteria should assure a consistent particle size distribution in terms of the percentage of total particles in given size ranges. The median, upper, and/or lower particle size limits should be well-defined. Acceptance criteria should be set based on the observed range of variation, and should take into account the particle size distribution of batches that showed acceptable performance in vivo, as well as the intended use of the product. If alternative sources of drug substance are proposed, evidence of equivalence should include appropriate physical characterisation and in vitro performance studies (see also Drug Product Pharmaceutical Development).

3. DRUG PRODUCT PHARMACEUTICAL DEVELOPMENT

Pharmaceutical development studies are conducted to establish that the dosage form, formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate and result in acceptable product performance.

It is generally expected that these tests be conducted on more than one batch, so that batch variability is taken into account. For products packaged in container closure systems that also serve as the device for administration, tests that involve delivery of the formulation should also be conducted on more than one batch of the container closure system components. In the case of multiple strengths and
multiple package sizes, a bracketing and/or matrixing design may be used to limit the number of test samples necessary. Justification should be provided.

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. It is not necessary to test all batches used in clinical studies, but batches used in pivotal clinical studies should be sufficiently characterised to support the specifications for the drug product.

3.1 Inhalation Products

The following tests are normally conducted to characterise inhalation products. Not all tests are necessary for all types of inhalation products, as noted in Table 1. However, any of the development tests may be applicable to any product, depending on the labelled instructions for use (e.g., shaking tests for certain dry powder inhalers). Moreover, depending on the operational characteristics of the inhaler device, additional studies relevant to the performance of the drug product may be necessary.
<table>
<thead>
<tr>
<th>Pharmaceutical Development Study</th>
<th>Pressurised Metered Dose Inhalers</th>
<th>Dry Powder Inhalers</th>
<th>Products for Nebulisation</th>
<th>Metered Dose Nebulisers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Device-Metered</td>
<td>Pre-Metered</td>
<td>Single Dose</td>
<td>Multi-Dose</td>
</tr>
<tr>
<td>(a) Minimum fill justification</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>(b) Extractables / Leachables</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>(c) Dose uniformity &amp; fine particle mass through container life</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>(d) Dose uniformity &amp; fine particle mass over flow range</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>(e) Fine particle mass with spacer use</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>(f) Single dose fine particle mass</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>(g) Individual stage particle size distribution</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes**</td>
</tr>
<tr>
<td>(h) Actuator deposition</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>(i) Droplet size distribution and drug output</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>(j) Shaking requirements</td>
<td>Yes**</td>
<td>No</td>
<td>No</td>
<td>Yes**</td>
</tr>
<tr>
<td>(k,l) Initial &amp; re-priming requirements</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>(m) Cleaning requirements</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>(n) Low temperature performance</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>(o) Performance after temperature cycling</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Table 1: Pharmaceutical Development Studies for Inhalation Products

<table>
<thead>
<tr>
<th>Pharmaceutical Development Study</th>
<th>Pressurised Metered Dose Inhalers</th>
<th>Dry Powder Inhalers</th>
<th>Products for Nebulisation</th>
<th>Metered Dose Nebulisers</th>
</tr>
</thead>
<tbody>
<tr>
<td>(p) Compatibility</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>(q) Preservative efficacy</td>
<td>No</td>
<td>No</td>
<td>No*</td>
<td>Yes</td>
</tr>
<tr>
<td>(r) Effect of moisture</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>(s) Physical characterisation</td>
<td>Yes**</td>
<td>Yes</td>
<td>Yes**</td>
<td>Yes**</td>
</tr>
<tr>
<td>(t) Robustness</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>(u) Device development</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Single dose products for nebulisation are expected to be sterile and preservative-free.
** For suspensions

(a) Minimum Fill Justification

A study should be conducted to demonstrate that the individual container minimum fill, as defined by the drug product manufacturing process, is sufficient to provide the labelled number of actuations. The final doses (as defined by the label claim) should meet the drug product specification limits for delivered dose uniformity and fine particle mass.

The fill tolerance of pre-metered products should be justified in relation to delivered dose uniformity and fine particle mass.

(b) Extractables / Leachables

A study should be conducted to determine the extractables profile from the container closure components that are in contact with the formulation during storage and/or use. Details and justification of the study design (e.g., solvents used, temperature, storage time) and the results should be provided. Identification of the compounds should be attempted and safety assessments should be conducted. A cross-reference to the data presented in Module 4 (Safety) should be included here.

It should be determined whether any of the extractables are also leachables present in the formulation at the end of the shelf life of the product or to the point equilibrium is reached, if sooner. Depending on the levels and types of compounds detected, consideration should be given to including a test and limits for leachables in the drug product specification. If a correlation between extractable and leachable profiles can be established, control of leachables could be accomplished via testing and limits on extractables. If there are no safety concerns with the type and level of leachables detected, routine monitoring of leachables would not be necessary.

(c) Delivered dose uniformity and fine particle mass through container life

A study should be conducted to demonstrate the consistency of the minimum delivered dose and the fine particle mass through the life of the container from the first (post-priming) dose until the last
labelled dose. The containers should be used and tested according to the information for the patient with respect to storage orientation and cleaning requirements, as well as minimum dosing interval. At least ten doses from the combination of the beginning, middle, and end of the container should be tested. A sufficient number of containers should be tested in order to also evaluate intra-batch variability.

The doses obtained should meet the drug product specification limits for delivered dose uniformity and fine particle mass.

The doses between the last labelled dose and the last container exhaustion dose should also be tested for delivered dose uniformity and fine particle mass, and information on the tail-off profile should be provided. At least three containers from two different batches should be investigated. This testing may be waived if the container contains a locking mechanism that prevents dosing beyond the labelled number of doses.

(d) Delivered dose uniformity and fine particle mass over patient flow rate range

A study should be conducted to demonstrate the consistency of the minimum delivered dose and the fine particle mass over the range of flow rates achievable by the intended patient population (through the device), at constant volume. The range of flow rates should be justified in relation to clinical studies or published data for the same device.

For each flow rate (minimally the minimum, median, and maximum achievable rate), the results obtained should be compared against the drug product specification limits for delivered dose uniformity and fine particle mass.

Depending on the results of this study, consideration should be given to providing information on the effect of flow rate on the performance of the product to health care professionals.

(e) Fine particle mass with spacer/holding chamber use

For inhalation products that may be administered with a spacer or holding chamber, a study should be conducted to determine whether the use of the spacer or holding chamber changes the fine particle mass. The fine particle mass should be tested before and after cleaning the spacer or holding chamber according to the instructions provided with the device.

Any differences in fine particle mass should be assessed for their clinical relevance (e.g. by clinical data obtained with the spacer or holding chamber). See also Region-Specific Appendices III: Devices, Spacers and Holding Chambers (European Union only).
(f) Single dose fine particle mass

The fine particle mass should be routinely determined using the minimum recommended dose. If the fine particle mass test included in the drug product specification uses a sample size greater than the minimum recommended dose, a study should be conducted to demonstrate that the sample size used routinely provides results equivalent to those obtained using the minimum recommended dose.

The fine particle mass of one dose should be determined according to the drug product specification fine particle mass method, modified only as necessary to accommodate the reduced sample size. Stage pooling prior to analysis is acceptable. If this study is not feasible due to the sensitivity of the analytical method, data supporting this claim should be provided.

The results obtained should be compared to fine particle mass results obtained according to the unmodified fine particle mass method for the same batches. Any differences should be assessed for their significance.

(g) Individual stage particle size distribution

To allow an assessment of the complete profile of the product used in in vivo (pivotal clinical and/or comparative bioavailability) studies, individual stage particle size distribution data should be provided for the batches used in these studies, as well as data on batches representative of the commercial process.

Using a multistage impactor or impinger, the drug mass on each stage and the cumulative mass undersize a given stage should be determined rather than the percentage of emitted dose (or other derived parameter) as these can hide variations in delivered dose. A plot of cumulative percentage less than a stated cut-off diameter versus cut-off diameter should usually be provided. From this, the Mass Median Aerodynamic Diameter (MMAD) and Geometric Standard Deviation (GSD) may be determined, if appropriate (in the case of log-normal distribution). Mass balance reconciliation should also be considered.

When a range of different strengths is proposed, proportionality in individual stage particle size distribution and fine particle mass should be considered.

(h) Actuator deposition

The amount of drug deposited on the actuator should be determined and, where applicable, demonstrated to be consistent with any correction factor used to support ex-valve label claims.

(i) Droplet size distribution and drug output

To allow an assessment of the complete profile of the product used in in vivo (pivotal clinical and/or comparative bioavailability) studies, droplet size distribution, output rate, and total drug output (i.e. total dose delivered to the patient) results should be provided for the batches used in these studies. A validated method, such as laser diffraction, should be employed. The aerosol should be generated with the nebuliser system(s) and settings used in the in vivo studies.

(j) Shaking requirements

For products requiring shaking before use, a study should be conducted to demonstrate that the shaking instructions provided to the consumer are adequate. The possibility of excessive shaking leading to foaming and inaccurate dosing should be examined by testing the delivered dose uniformity.
(k) Initial priming of the container

A study should be conducted to determine the number of actuations that should be fired to waste (priming actuations) prior to the consumer using the product for the first time. Containers should be stored in various orientations prior to the initiation of the study in order to determine the effect of orientation. The length of storage prior to conducting the study should be indicated and justified.

The number of priming actuations required until the subsequent doses meet the drug product specification limits for delivered dose uniformity should be determined.

Priming instructions should be provided to the health care professional and the consumer.

(l) Re-priming of the container

A study should be conducted to determine the length of time that the product may be stored without use (after initial priming) before re-priming, as well as the number of re-priming actuations required. Containers should be stored in various orientations prior to and during the study in order to determine the effect of orientation.

The maximum length of time that the product may be stored before the subsequent doses no longer meet the drug product specification limits for delivered dose uniformity should be determined. Multiple time points should be used. The number of re-priming actuations required until the subsequent doses meet the drug product specification limits for delivered dose uniformity should also be determined.

Since most products demonstrate acceptable performance after storage for up to one week without re-priming, any requirement for more frequent re-priming may adversely affect patient compliance and should therefore be fully warranted and justified.

Re-priming instructions, including any necessary instructions with respect to storage orientation, should be provided to the health care professional and the consumer.

(m) Cleaning requirements

Delivered dose uniformity and fine particle mass or droplet size distribution data to support the recommended cleaning instructions provided to the health care professional and the consumer (including method and frequency) should be provided. The study should be conducted under conditions of normal patient usage, in accordance with recommendations for priming, dosing intervals, and typical dosing regimen.

Since most products demonstrate acceptable performance with a weekly cleaning regimen, any requirement for more frequent cleaning may adversely affect patient compliance and should therefore be fully warranted and justified.

(n) Low temperature performance

A study should be conducted to determine the effect of low temperature storage on the performance of the product. Containers should be stored in various orientations for at least 3 hours at a temperature below freezing (0°C), and then immediately tested.

The number of actuations required until the subsequent doses meet the drug product specification limits for delivered dose uniformity and fine particle mass should be determined. If the product does not perform satisfactorily (e.g., re-priming actuations required exceed the number required after
storage for one week), an additional study should be conducted to determine the method and length of
time needed to adequately warm the containers so that satisfactory performance is achieved.

Instructions regarding cold temperature use should be provided to the health care professional and the
consumer. If this study is not conducted, information on how and how long to warm the container
should be provided to the health care professional and the consumer.

(o) Performance after temperature cycling

A study should be conducted to determine the effect of temperature cycling on the performance of the
product. Containers should be stored in various orientations and cycled between recommended storage
conditions and a temperature below freezing (0°C). For suspension products cycling between the
recommended storage conditions and a high temperature should be considered. Storage time should be
at least 24 hours under each condition, and containers should be stored under each condition at least
five times.

The containers should be examined visually for any obvious defects, and tests such as leak rate, weight
loss, delivered dose uniformity, fine particle mass, related substances and moisture content should be
performed. Any changes from initial results should be assessed for their significance.

(p) Compatibility

If the product is to be diluted prior to administration, compatibility should be demonstrated with all
diluents over the range of dilution proposed in the labelling. These studies should preferably be
conducted on aged samples, and should cover the duration of storage of the diluted product indicated
in the labelling. Where the labelling specifies co-administration with other drugs, compatibility should
be demonstrated with respect to the principal drug as well as the co-administered drug.

Parameters such as precipitation, pH, droplet size distribution, output rate and total drug output should
be tested, and differences from the original product should be assessed for their significance.

(q) Preservative efficacy

For products containing a preservative, a study should be conducted to demonstrate the effectiveness
of the preservative at the lower specification limit for the preservative concentration.

(r) Effect of moisture

The effect of moisture on product performance should be investigated during development. For pre-
metered products using capsules, special attention should be paid to brittleness of the capsules under
various humidity conditions.

(s) Physical characterisation

Physical characteristics such as solubility, size, shape, density, rugosity, charge, and crystallinity of
the drug substance and/or excipients may influence the homogeneity and reproducibility of the
finished product. Development studies should include physical characterisation of drug substance and
excipients, relevant to their effect on the functionality of the product.

If applicable, the effect of pre-processing the material (e.g. micronisation) on the physical
characteristics should be evaluated.

(t) Robustness
The product performance should be investigated under conditions to simulate use by patients. This includes activating the device at the frequency indicated in the instructions for use. Carrying the inhaler between use and simulation of dropping the device, etc. should be considered.

Vibrational stability of powder mixtures should be demonstrated, in order to simulate vibrations during transport and use. Assessment of vibrational stability following exposure of powder blends to conditions of elevated temperature and humidity can be useful in assessing potential problems in use. Significant variations in the delivered dose and/or fine particle mass should be fully discussed in terms of the safety and efficacy of the product.

(u) Device development

The development of the device should be described. Any changes implemented in the design (e.g. change of component materials) and/or manufacturing process of the device (e.g. scale up from single cavity to multiple cavity tooling) during the development of the product should be discussed in terms of the impact on the product performance characteristics (e.g. delivered dose, fine particle mass, etc.). If prototype devices were used in clinical studies, appropriate in vitro data should be provided to demonstrate the equivalence of the prototype(s) with the product intended for marketing.

For device-metered dry powder inhalers, safeguards to prevent inadvertent multiple dose metering (and subsequent inhalation by the patient) should be demonstrated.

For breath-activated devices, data should be provided to demonstrate that all target patient groups are capable of triggering the device. This could be evaluated as part of the clinical programme during patient handling studies. The triggering mechanism should be well characterised as part of the device development programme.

For dry powder inhaler reservoir systems each unit should have 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. Inclusion of dose counters is also encouraged for other multiple dose products.

3.2 Nasal Products

The following tests are normally conducted to characterise nasal products. Not all tests are necessary for all types of nasal products, as noted in Table 2.

Minimum fill justification, extractables/leachables, delivered dose uniformity through container life, actuator deposition, shaking requirements, initial and re-priming requirements, cleaning requirements, low temperature performance, performance after temperature cycling, preservative efficacy, effect of moisture, physical characterisation, robustness, and device development should be studied as discussed in Section 3.1, with the exception of tests for fine particle mass. With regard to droplet / particle size distribution, full characterisation of the product should be provided. It should be demonstrated that deposition of the product is localised in the nasal cavity.

Table 2: Pharmaceutical Development Studies for Nasal Products

<table>
<thead>
<tr>
<th>Pharmaceutical Development Study</th>
<th>Pressurised Metered Dose Nasal Sprays</th>
<th>Nasal Powders (Device-Metered)</th>
<th>Nasal Liquids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum fill justification</td>
<td>Yes</td>
<td>Yes</td>
<td>Single Use Drops</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Table 2: Pharmaceutical Development Studies for Nasal Products

<table>
<thead>
<tr>
<th>Pharmaceutical Development Study</th>
<th>Pressurised Metered Dose Nasal Sprays</th>
<th>Nasal Powders (Device-Metered)</th>
<th>Nasal Liquids</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Single Use Drops</td>
</tr>
<tr>
<td>Extractables / Leachables</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Delivered dose uniformity through container life</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Actuator deposition</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Droplet / particle size distribution</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Shaking requirements</td>
<td>Yes**</td>
<td>No</td>
<td>Yes**</td>
</tr>
<tr>
<td>Initial &amp; re-priming requirements</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cleaning requirements</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Low temperature performance</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Performance after temperature cycling</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Preservative efficacy</td>
<td>No</td>
<td>No</td>
<td>No*</td>
</tr>
<tr>
<td>Effect of moisture</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Physical characterisation</td>
<td>Yes**</td>
<td>Yes</td>
<td>Yes**</td>
</tr>
<tr>
<td>Robustness</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Device development</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Single use nasal drops are expected to be sterile and preservative-free.
** For suspensions

4. DRUG PRODUCT MANUFACTURE
For clarity, the formulation of the product should include the concentration of the drug substance in the formulation, the fill amount, and the target delivery amount.

The manufacturing process of the drug product, including all filling and packaging operations, should be described for each strength and each container closure system (e.g., number of actuations). Single use aqueous products should normally be sterile and preservative-free.

The manufacturing process for all products should be validated to ensure the homogeneity of the formulation throughout the filling process during routine production and include controls assuring that all containers are within an appropriate fill volume or fill weight range, and that the closure system is applied correctly (e.g., crimp dimensions and leak testing for pressurised products, blister sealing for dry powder inhalers, torque measurement for screw thread pumps). All products should also have a process control for performance testing of the actuation release mechanism (e.g., shot weight) of each unit where appropriate.

Any equilibration time allowed for pressurised products before release testing should be specified and justified along with other aspects of the manufacturing process.

5. EXCIPIENTS
Besides the usual pharmacopoeial requirements, additional tests to characterise the material used should be included in the specifications as appropriate.

For dry powder inhalers for example, a test and suitable multi-point particle size test should be included for the excipient(s) (e.g. lactose) or where appropriate, for granules of excipients and/or drug substance. The limits for this test should be qualified by the results of batches used to produce drug product for in vivo (pivotal clinical and/or comparative bioavailability) studies although in vitro data (from multistage impaction / impinger) may suffice to demonstrate the suitability of the extremes of the limits.

Control of other physical parameters may be achieved by specification of the grade of each material used. For excipients which have physical properties that cannot be easily controlled (but are relevant for the drug product performance), the source should be limited to a single, validated supplier. Alternatively, the suitability of different suppliers should be demonstrated with in vitro data for finished product manufactured with different batches from each source. If these conditions are met, no specification for physical characteristics, other than particle size distribution (if relevant), is necessary.

In addition, control of microbial quality should be considered.

5.1 Pharmacopoeial Excipients
Excipients that have a well-established history of use in inhalation and nasal products, and are tested according to a monograph of an accepted pharmacopoeia, may be used without providing safety data on the excipient alone, provided that the amounts used are common for the route of administration. Any excipient without a well-established history of use in inhalation and nasal products must be demonstrated to be safe when administered by the new route of administration. The type of safety data needed may be discussed with the authority prior to filing.

5.2 Non-pharmacopoeial Excipients
Excipients that are not tested according to an accepted pharmacopoeial monograph must be demonstrated to be safe when administered by the inhalation or nasal route of administration, as appropriate. The excipient specification tests and limits, particularly with respect to purity, should be established based on results for batches used in safety studies. The type of safety data needed may be discussed with the authority prior to filing.

In addition to the specification, information on the manufacture of the excipient may also be necessary. The extent of manufacturing information needed may be discussed with the authority prior to filing.
6. DRUG PRODUCT SPECIFICATION(S)

6.1 Inhalation Products

The following list includes the tests normally included in the drug product specifications for inhalation products. Different tests and limits may apply at release versus shelf life; differences should be clearly described and justified.

Not all tests are necessary for all types of inhalation products, as noted in Table 3.

Note that standard drug product specification tests (e.g., identification, degradation products, pH) have not been included as these are not specific to inhalation products. However, it is expected that these tests be included. Other guidance documents should be consulted in this regard.

Table 3: Drug Product Specification Tests for Inhalation Products

<table>
<thead>
<tr>
<th>Drug Product Specification Test</th>
<th>Pressurised Metered Dose Inhalers</th>
<th>Dry Powder Inhalers</th>
<th>Products for Nebulisation</th>
<th>Metered Dose Nebulisers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Device-Metered</td>
<td>Pre-Metered</td>
<td>Single Dose</td>
<td>Multi-Dose</td>
</tr>
<tr>
<td>(a) Description</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>(b) Assay</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>(c) Moisture content</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>(d) Delivered dose uniformity</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>(e) Content uniformity / Uniformity of dosage units</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>(f) Fine particle mass</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes**</td>
</tr>
<tr>
<td>(g) Leak rate</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>(h) Weight loss</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>(i) Microbial limits</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>(j) Sterility</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes*</td>
</tr>
<tr>
<td>(k) Leachables</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>(l) Preservative content</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No*</td>
</tr>
</tbody>
</table>
Table 3: Drug Product Specification Tests for Inhalation Products

<table>
<thead>
<tr>
<th>Drug Product Specification Test</th>
<th>Pressurised Metered Dose Inhalers</th>
<th>Dry Powder Inhalers</th>
<th>Products for Nebulisation</th>
<th>Metered Dose Nebulisers</th>
</tr>
</thead>
<tbody>
<tr>
<td>(m) Number of actuations per container</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

* Single dose products for nebulisation are expected to be sterile and preservative-free.
** For suspensions

(a) Description

A description of both the formulation and the full device (e.g., including actuator) should be given where applicable. For products for nebulisation, the immediate packaging should be described (e.g., translucent LDPE nebul).

(b) Assay

For multi-dose products, the amount of drug substance should be determined per weight unit or per volume unit, as applicable. For single dose products, the assay should be expressed as mass per dosage unit. The usual assay limits for medicinal products apply.

The amount of drug substance in one actuation should also be determined by calculating the mean of the content uniformity or delivered dose uniformity test results, with corrections as necessary to convert from “per dose” amounts to “per actuation” amounts. Limits of ± 15% of the label claim apply.

(c) Moisture Content

The limit for moisture content should be established based on results seen in stability studies. If the results are stable throughout the shelf life of the product, or if any changes in moisture content do not result in changes to any other parameters, it may be acceptable to omit this test from the specification; this should be fully explained in the Justification of Specification(s) section.

(d) Delivered Dose Uniformity

The delivered dose uniformity test should be conducted according to an accepted pharmacopoeial method. Limits applied should be consistent with the pharmacopoeia, with adaption as necessary to test both intra- and inter-device variability.

The use of weight in lieu of content uniformity may be acceptable for solution formulations; justification should be provided.

(e) Content Uniformity / Uniformity of Dosage Units

Content uniformity should be investigated on samples removed from the containers as per the instructions provided to consumers and health care professionals. Acceptance limits should be justified, taking into consideration pharmacopoeial requirements.
The use of weight in lieu of content uniformity may be acceptable for solution formulations; justification should be provided.

(f) Fine Particle Mass

The fine particle mass test should be conducted using a validated multistage impactor or impinger method. It is normally considered acceptable to set upper and lower limits on the results of pooled stages corresponding to a particle size distribution of less than 5 µm, although alternative limits may be found acceptable with adequate justification. The drug mass should be reported rather than the percentage of emitted dose (or other derived parameter). Additional criteria may be appropriate such as grouped stages or limits for mass median aerodynamic diameter (MMAD) and / or geometric standard deviation (GSD) if the fine particle mass alone is insufficient to fully characterise the particle size distribution of the therapeutic dose. Control of the particle size distribution above 5 µm may be necessary depending on the relevance of this fraction for the therapeutic index of the product.

In all cases, limits should be qualified by the fine particle mass results for batches used in in vivo (pivotal clinical and/or comparative bioavailability) studies and should be reported on a per actuation basis.

(g) Leak Rate

A leak rate test and limits should be included in the specification.

(h) Weight loss

A test and limits for weight loss during the shelf life should be included in the specification. If the results are stable throughout the shelf life of the product, it may be acceptable to omit this test from the specification; this should be fully explained in the Justification of Specification(s) section.

(i) Microbial Limits

Microbial limit testing should be conducted according to an accepted pharmacopoeial test.

(j) Sterility

Sterility testing should be conducted according to an accepted pharmacopoeial test.

(k) Leachables

Depending on the results of the pharmaceutical development study on extractables and leachables (see Section 3.1(b) Drug Product Pharmaceutical Development: Inhalation Products), a test and qualified limits for leachables should be included in the specification.

(l) Preservative content

Preservative assay testing should be conducted.

(m) Number of actuations per container

The number of actuations per container should be demonstrated to be no less than the labelled number of actuations.

6.2 Nasal Products
The following list includes the tests normally included in the drug product specifications for nasal products. Different tests and limits may apply at release versus shelf life; differences should be clearly described and justified.

Not all tests are necessary for all types of nasal products, as noted in Table 4.

Note that standard drug product specification tests (e.g., identification, degradation products, pH) have not been included as these are not specific to nasal products. However, it is expected that these tests be included. Other guidance documents should be consulted in this regard.

The tests for description, assay, moisture content, delivered dose uniformity, content uniformity, leak rate, weight loss, microbial limits, sterility, preservative content, and number of actuations per container are as described in Section 6.1. In addition to these tests, droplet / particle size distribution testing should be conducted using a validated method, such as laser diffraction. The limits should include an allowed range for the median diameter and a limit on d10. It is normally expected that the vast majority of droplets / particles are larger than 10 µm to avoid inhalation, however, limits should be qualified by the droplet / particle size distribution results for batches used in in vivo (pivotal clinical and/or comparative bioavailability) studies.

**Table 4: Drug Product Specification Tests for Nasal Products**

<table>
<thead>
<tr>
<th>Drug Product Specification Test</th>
<th>Pressurised Metered Dose Nasal Sprays</th>
<th>Nasal Powders (Device-Metered)</th>
<th>Nasal Liquids</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single Use Drops</td>
<td>Multiple Use Drops</td>
<td>Sprays</td>
</tr>
<tr>
<td>Description</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Assay</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Moisture content</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Delivered dose uniformity</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Content uniformity / Uniformity of dosage units</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Droplet / particle size distribution</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Leak rate</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Weight loss</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Microbial limits</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sterility</td>
<td>No</td>
<td>No</td>
<td>Yes*</td>
</tr>
<tr>
<td>Preservative content</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4: Drug Product Specification Tests for Nasal Products

<table>
<thead>
<tr>
<th>Number of actuations per container</th>
<th>Yes</th>
<th>Yes</th>
<th>No</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
</table>

* Single use nasal drops are expected to be sterile and preservative-free.

7. DRUG PRODUCT CONTAINER CLOSURE SYSTEM

In addition to standard container closure system specification tests (e.g., identification, dimensions), the specifications should include further tests to confirm reproducible drug delivery. For example, for pressurised metered dose products for inhalation or nasal use, specifications should include tests such as shot weight of individual sprays and actuator orifice length and diameter.

The composition of all container closure system components should be provided and should comply with relevant standards in relation to their intended use.

For coated canisters and/or valves, the complete composition of the coating and the procedure (including process controls) used in the coating process should be provided.

For plastic components, in addition to the resin used, any additives included should also be described.

8. DRUG PRODUCT STABILITY

All inhalation and nasal products should be tested on stability against the stability-indicating tests included in the drug product specification, according to applicable guidance documents.

Containers should be stored in various orientations during the study in order to determine the effect of orientation. Data should be presented separately for each orientation.

If the product includes secondary packaging in order to protect it from light and/or humidity (e.g., dry powder inhaler inside a foil overwrap), the length of time that the product may be used after the protective packaging has been removed should be supported by stability results. The studies should involve removing the product from the protective packaging close to the end of its shelf life and testing the exposed product against the drug product specifications.

Information on the use of the product once the protective packaging has been removed should be provided to the consumer.

9. GLOSSARY

**activation:** the act of setting in motion the drug delivery device

**actuation:** the release of drug from the drug delivery device by a single activation (e.g., mechanical or breath).

**delivered dose:** the quantity of drug substance that is available to the user, ex-device, on a per dose basis.

**device:** the component(s) of the container closure responsible for delivering the drug to the respiratory tract (inhalation product) or the nasal and/or pharyngeal region (nasal product).
dose: quantity of the drug substance to be administered at one time, as specified in the information provided to consumers and health care professionals; also, the number of actuations providing that quantity of drug substance.

dosing interval: the recommended length of time between doses, as specified in the information provided to consumers and health care professionals.

dry powder inhaler (DPI), an inhalation product containing a reservoir of powder which is device-metered: measured into individual actuations by the device.

dry powder inhaler (DPI), an inhalation product containing pre-measured actuations, usually pre-metered: in capsules or blister packaging.

ex-actuator: not including the (quantity of drug substance deposited on the) actuator

extractables: compounds which may be extracted from the container closure system by using strong solvents at high temperatures.

fine particle mass: the quantity of drug substance in an inhalation product that is generally considered to be of a size capable of penetrating the lung during inhalation (approximately 5 µm and smaller), on a per actuation basis.

Geometrical Standard Deviation (GSD): derived from the plot of the cumulative percentage of mass less than the stated cut-off diameter versus the cut-off diameter by the equation:

\[(D_{84.13\%} / D_{15.87\%})^{1/2}\]

inhalation product: a drug product (including the device) whose intended site of deposition is the respiratory tract. The site of action may be local or systemic.

leachables: compounds which may leach from the container closure system into the formulation under normal conditions of storage and use.

metered dose: the quantity of drug substance contained in the device metering chamber or pre-measured unit

metered dose nebuliser: portable, inhaler device containing an aqueous solution or suspension, which delivers one dose in one breath

minimum delivered dose: the smallest recommended quantity of drug substance available to the patient

Mass Median Aerodynamic Diameter (MMAD): the diameter of a sphere of unit density having the same terminal settling velocity as the particle at issue; derived from the plot of the cumulative percentage of mass less than the stated cut-off diameter versus the cut-off diameter by determination of the diameter at 50.00%.
<table>
<thead>
<tr>
<th><strong>nasal product:</strong></th>
<th>a drug product (including the device) whose intended site of deposition is the nasal and/or pharyngeal region. The site of action may be local or systemic.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>nebuliser:</strong></td>
<td>a mechanical device used to atomize liquids for inhalation.</td>
</tr>
<tr>
<td><strong>pressurised metered dose inhaler:</strong></td>
<td>an inhalation product containing one or more propellants in a pressurised delivery device.</td>
</tr>
<tr>
<td><strong>pressurised metered dose nasal spray:</strong></td>
<td>product for nasal administration containing one or more propellants in a pressurised delivery device.</td>
</tr>
<tr>
<td><strong>product for nebulisation:</strong></td>
<td>an inhalation product administered as a liquid via a commercially marketed nebuliser.</td>
</tr>
<tr>
<td><strong>spray:</strong></td>
<td>see actuation</td>
</tr>
<tr>
<td><strong>target delivered dose:</strong></td>
<td>the quantity of drug substance expected to be released from the device in the number of actuations equivalent to a dose.</td>
</tr>
<tr>
<td><strong>target delivery amount:</strong></td>
<td>the quantity of drug substance expected to be released from the device (i.e., ex-actuator or ex-device) in one actuation.</td>
</tr>
<tr>
<td><strong>therapeutic index:</strong></td>
<td>the ratio of the dose resulting in toxicity to the dose required to achieve the desired therapeutic effect.</td>
</tr>
</tbody>
</table>
JOINT HEALTH CANADA - EUROPEAN UNION GUIDANCE
PHARMACEUTICAL QUALITY OF INHALATION AND NASAL PRODUCTS

EUROPEAN UNION APPENDIX I:
GENERIC PRODUCTS

For generic products, essential similarity is claimed to an original/reference medicinal product (innovator product). Therapeutic equivalence to the innovator product must be substantiated by in vivo and/or in vitro studies (see Points to Consider on the Requirements for Clinical Documentation for Orally Inhaled Products). In all cases, the comparability of the generic and innovator products must be demonstrated in vitro as indicated below.

Inhalation Products
For Pressurised Metered Dose inhalers, Dry Powder Inhalers, and Metered Dose Nebulisers
comparative in vitro data of the generic product versus the innovator product must be provided on the complete individual stage particle size distribution profile using a multistage impactor/impinger. If relevant (flow rate dependency), a range of flow rates should be tested. In addition, the delivered dose must be compared.

For Products for Nebulisation the complete droplet size distribution of the generic product must be compared with the innovator product using a validated method, such as laser diffraction. In addition, the output rate and total drug output should be compared. If applicable, the aerosol must be generated with the nebuliser system(s) and settings used in vivo. Comparisons may be waived for generic Solutions for Nebulisation having the same qualitative and quantitative composition as the innovator product. For Suspensions for Nebulisation, the individual stage particle size distribution should also be compared.

Any differences beyond normal analytical variability should be accompanied by a rationale as to why the differences will not result in different deposition and/or absorption characteristics.

Furthermore, it is recognised that only limited or no data may be available on batches used in vivo. The following remarks on various drug product pharmaceutical development sections and on the excipients section are therefore made:

3.1.(b) Extractables/Leachables
With regard to the extractables/leachables profile, safety assessments may also be based on profile comparison of the generic product versus the innovator product, where this is justified by the composition of packaging.

3.1.(d) Delivered dose uniformity and fine particle mass over patient flow range
If no in vivo studies were performed, the range of flow rates investigated should be justified.

3.1.(g) Individual stage particle size distribution
If no in vivo studies were performed, the results of batches representative of the commercial process (e.g. in terms of batch size, manufacturing method of the inhaled preparation and the device) should be compared with the batches used for substantiation of in vitro equivalence.

3.1.(i) Droplet size distribution and drug output
If no in vivo studies were performed, the results of batches representative of the commercial process should be compared with the batches used for substantiation of in vitro equivalence.

5.1 Pharmacopoeial Excipients
If no in vivo studies were performed, any limits for relevant parameters (such as particle size distribution and shape of the carrier for dry powder preparations) must be based on the batches used for substantiation of in vitro equivalence.
Nasal Products

For generic nasal products claiming essential similarity to an originator/innovator product, studies required to demonstrate therapeutic equivalence may depend on the intended site of action of the active substance (local or systemic).

The Note for Guidance on clinical requirements for locally applied locally acting products containing known constituents (CPMP/EWP/239/95) and Note for Guidance on Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) should be consulted.

For Nasal Sprays comparative data of the generic product versus the innovator product must be provided on the complete droplet size distribution using a validated method, such as laser diffraction. In addition, for Nasal Sprays and Nasal Powders the delivered dose must be compared. For Nasal Drops a comparison of the droplet volume of the generic product versus the innovator product should be provided.

Any differences beyond normal analytical variability should be accompanied by a rationale as to why the differences will not result in different deposition and/or absorption characteristics.

Furthermore, it is recognised that only limited or no data may be available on batches used in vivo. With respect to extractables/leachables, droplet size distribution, and excipients the same remarks as for generic Inhalation Products are applicable.
Besides the general requirements, several Inhalation and Nasal Products specific information should be included in the Summary of Product Characteristics.

**Inhalation Products**

*Section 2. Qualitative and Quantitative Composition*
For Pressurised Metered Dose Inhalers, Dry Powder Inhalers, and Metered Dose Nebulisers the content per actuation can be expressed either ex valve (metered dose) or ex actuator (delivered dose). All products containing new chemical entities and products containing known drug substances used in inhalation products for the first time should be labelled with the delivered dose or an appropriate alternative (e.g. fine particle mass) where agreed with the regulatory authorities. For existing products current practice in each EU member state should be followed. In any case, it should be clearly stated if the labelled claim is expressed as metered dose (ex valve), as delivered dose (ex actuator) or an appropriate alternative.

*Section 4.2 Posology and Method of Administration*
In view of the fact that different products of the same drug might be labelled with the same metered or delivered dose but have a different therapeutic effect due to differences in the fine particle mass compared to that of an established ‘brand leader’ it should be clearly stated if the product is not interchangeable with other marketed products.

The instructions for use should be clearly described, including directions with respect to the following items (if applicable):
- shaking requirements
- cold temperature use
- the need for priming and re-priming
- the effect of flow rate on the performance of the product
- orientation of the inhaler during inhalation
- the use of any specific spacer/holding chamber
- cleaning requirements, including instructions for any specific spacer/holding chamber

For Products for Nebulisation the nebuliser system(s) and settings that were proven to be effective and safe *in vivo* must be indicated, including information on the droplet size distribution, output rate and total drug output.

*Section 6.4 Special Precautions for Storage*
For Pressurized Metered Dose Inhalers 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.'
Nasal Products

Section 2. Qualitative and Quantitative Composition
For Pressurised Metered Dose Nasal Sprays, Nasal Sprays, and Nasal Powders the content per actuation can be expressed either ex valve (metered dose) or ex actuator (delivered dose). All products containing new chemical entities and products containing known drug substances used in inhalation products for the first time should be labeled with the delivered dose, but for existing products current practice in each EU member state should be followed. In any case, it should be clearly stated if the labeled claim is expressed as metered dose (ex valve) or as delivered dose (ex actuator). Nasal Drops should be labeled with the amount of drug per drop.

Section 4.2 Posology and Method of Administration
The instructions for use should be clearly described, including directions with respect to the following items (if applicable):
- shaking requirements
- cold temperature use
- the need for priming and re-priming
- cleaning requirements

Section 6.4 Special Precautions for Storage
For Pressurised Metered Dose Nasal Sprays 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.’
In Europe all devices have to fulfil the “Essential Requirements” as outlined in Annex 1 of Council Directive 93/42 EEC. For devices that are refillable a CE mark is required. Evidence of this accreditation should be presented, along with data to support the information provided in the Summary of Product Characteristics and Patient Information Leaflet in relation to the shelf life of the device (before and during use), storage conditions (where relevant) and the number of times it can be refilled.

When a spacer or holding chamber is required for administration of the product to a particular patient population (e.g. paediatrics, administration of high dose steroids), its use should be validated. Relevant information on the spacer/holding chamber must be given in the Summary of Product Characteristics (see also II Summary of Product Characteristics). In addition to in vitro studies, the suitability of the spacer should be supported by appropriately designed clinical studies. Any claims exceeding instructions for use and handling, e.g. reduction in the amount of large particles, must be supported by in vitro data.