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**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

**GUIDELINE ON THE PHARMACEUTICAL QUALITY OF INHALATION AND NASAL
PRODUCTS**

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Note: This Guideline has been prepared in collaboration with Health Canada and represents a harmonised guideline. It replaces the QWP Guidelines on pressurised Metered Dose Inhalation Products (pMDIs) and Dry Powder Inhalers (DPI) and is complementary to the existing Efficacy Working Party Guideline on Orally Inhaled Products (OIP). The final Guideline has been adapted to the EU template for Guidelines.

GUIDELINE ON THE PHARMACEUTICAL QUALITY OF INHALATION AND NASAL PRODUCTS

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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. The document outlines expected quality aspects of drug 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.

Only quality aspects specific to inhalation and nasal products are discussed, although the need for safety testing (e.g., for excipients and leachables) is also addressed. Additional quality aspects (e.g., impurities, process validation, stability testing, specifications) as well as safety and efficacy aspects, are described in other guidance documents, including ICH guidelines.

Detailed guidance on pharmaceutical development study designs (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, ISO standards). It is also recognised that the wide diversity of inhalation and nasal products with respect to formulation and delivery device characteristics necessitates some flexibility in testing methodology.

2. SCOPE

The document addresses new marketing authorisation applications (including for generic products) and does not outline expected quality aspects related to changes in existing inhalation and nasal products. However, the general principles described here should also be considered when making changes to existing products.

This guidance document has been developed for products containing drug substances of synthetic or semi-synthetic origin. However, the general principles described here should also be considered for other inhalation and nasal products.

This document includes products for administration of the drug substance to the lungs, such as pressurised metered dose inhalers, dry powder inhalers, products for nebulisation, and non-pressurised metered dose inhalers, as well as pressurised metered dose nasal sprays, nasal powders, and nasal liquids. Liquid inhalation anaesthetics and nasal ointments, creams and gels are excluded.

3. LEGAL BASIS

Directive 2001/83/EC, as amended.

4. MAIN GUIDELINE TEXT

4.1 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 particle sizing method (e.g., laser diffraction), with acceptance criteria set at multiple points across the size distribution, 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. Process capability and stability data may also be considered, provided the proposed acceptance criteria have been suitably qualified.

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).

4.2 DRUG PRODUCT PHARMACEUTICAL DEVELOPMENT

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

It is generally expected that the development tests be conducted on more than one batch, so that batch variability is taken into account. For a single strength and a single container closure system, testing two batches should be sufficient. For products packaged in container closure systems that also serve as the delivery device, tests that involve delivery of the formulation should also be conducted on more than one batch of the container closure system. 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.

If the tests described are not conducted due to the particular nature of the product or because assurance of the parameter has been established by another means, a justification for the omission should be provided.

4.2.1 Inhalation Products

The tests indicated in Table 4.2.1 are normally conducted to characterise inhalation products. Not all tests are necessary for all types of inhalation products, as noted in Table 4.2.1. 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 delivery device, additional studies relevant to the performance of the drug product may be necessary.

See Appendix I for additional information on pharmaceutical development testing of generic products. See Appendix II for additional information on how the pharmaceutical development testing links to the information for consumers and health care professionals.

Table 4.2.1 Pharmaceutical Development Studies for Inhalation Products

Pharmaceutical Development Study	Pressurised Metered Dose Inhalers	Dry Powder Inhalers		Products for Nebulisation		Non-Pressurised Metered Dose Inhalers
		Device-Metered	Pre-Metered	Single Dose	Multi-Dose	
(a) Physical characterisation	Yes*	Yes	Yes	Yes*	Yes*	Yes*
(b) Minimum fill justification	Yes	Yes	Yes	Yes	Yes	Yes
(c) Extractables / Leachables	Yes	No	No	Yes	Yes	Yes
(d) Delivered dose uniformity & fine particle mass through container life	Yes	Yes	Yes	No	No	Yes
(e) Delivered dose uniformity & fine particle mass over patient flow rate range	No	Yes	Yes	No	No	No
(f) Fine particle mass with spacer use	Yes	No	No	No	No	No
(g) Single dose fine particle mass	Yes	Yes	Yes	No	No	Yes
(h) Particle / droplet size distribution	Yes	Yes	Yes	Yes	Yes	Yes
(i) Actuator / mouthpiece deposition	Yes	Yes	Yes	No	No	Yes
(j) Drug delivery rate and total drug delivered	No	No	No	Yes	Yes	No
(k) Shaking requirements	Yes*	No	No	Yes*	Yes*	Yes*
(l,m) Initial & re-priming requirements	Yes	No	No	No	No	Yes
(n) Cleaning requirements	Yes	Yes	Yes	No	No	Yes

Table 4.2.1 Pharmaceutical Development Studies for Inhalation Products

Pharmaceutical Development Study	Pressurised Metered Dose Inhalers	Dry Powder Inhalers		Products for Nebulisation		Non-Pressurised Metered Dose Inhalers
		Device-Metered	Pre-Metered	Single Dose	Multi-Dose	
(o) Low temperature performance	Yes	No	No	No	No	No
(p) Performance after temperature cycling	Yes	No	No	No	No	Yes
(q) Effect of environmental moisture	Yes	Yes	Yes	No	No	No
(r) Robustness	Yes	Yes	Yes	No	No	Yes
(s) Delivery device development	Yes	Yes	Yes	Yes	Yes	Yes
(t) Preservative effectiveness / efficacy	No	No	No	Yes**	Yes**	Yes**
(u) Compatibility	No	No	No	Yes	Yes	No

* For suspensions.

** If a preservative is present.

4.2.1.1 Physical characterisation (CTD 3.2.P.2.1.1 and 3.2.P.2.1.2)

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.

4.2.1.2 Minimum Fill Justification (CTD 3.2.P.2.2.2)

For metered dose inhalers and device-metered dry powder inhalers, 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.

For pre-metered dry powder inhalers and products for nebulisation, the acceptance criteria for the fill volume and/or weight should be justified in relation to delivered dose uniformity and fine particle mass.

4.2.1.3 Extractables / Leachables (CTD 3.2.P.2.4)

For non-compendial plastic and for rubber container closure components that are in contact with the formulation during storage (e.g., valves), a study should be conducted to determine the extractables profile. Details and justification of the study design (e.g., solvents used, temperature, storage time) and the results should be provided. 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. The leachables profile should also be determined for compendial plastics and rubber container closure components.

For compounds that appear as leachables, identification should be attempted and safety assessments should be conducted in accordance with adequately established safety thresholds. A cross-reference to the data presented in Module 4 (Safety) should be included.

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, either on the components or on the raw materials if a correlation has been shown between the levels in the raw materials and components. If there are no safety concerns with the type and level of leachables detected, routine monitoring of leachables would not be necessary.

4.2.1.4 Delivered dose uniformity and fine particle mass through container life (CTD 3.2.P.2.4)

A study should be conducted to demonstrate the consistency of the minimum delivered dose (e.g., one or more actuations) and the fine particle mass through the life of the container from the first dose (post-priming dose for products with priming instructions) 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. It is generally expected that at least ten doses from the combination of the beginning, middle, and end of the container be tested.

The doses obtained should meet the drug product specification limits for delivered dose uniformity and fine particle mass. Non-conforming results should be explained.

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 where applicable. At least three containers from each of two different batches should be investigated. This testing may be waived if the container contains a lockout mechanism that prevents dosing beyond the labelled number of doses.

4.2.1.5 Delivered dose uniformity and fine particle mass over patient flow rate range (CTD 3.2.P.2.4)

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 (through the delivery device) achievable by the intended patient population, at constant volume. The range of flow rates should be justified in relation to clinical studies or published data for the same delivery device. The minimum (e.g., 10th percentile), median, and maximum (e.g., 90th percentile) achievable rate should be investigated.

Depending on the results of this study (e.g., if the minimum flow rate does not produce an acceptable dose), consideration should be given to providing information on the effect of flow rate on the performance of the product to health care professionals.

4.2.1.6 Fine particle mass with spacer/holding chamber use (CTD 3.2.P.2.4)

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. If the instructions accompanying the spacer or holding chamber include an in-use cleaning schedule (e.g., weekly cleaning), the fine particle mass should be tested before and after cleaning the spacer or holding chamber according to the instructions provided with the device. The fine particle mass test used for routine testing of the product may be altered to mimic patient performance with the spacer or holding chamber (e.g., a 2 second delay, tidal breathing).

Any differences in fine particle mass should be assessed for their clinical relevance, with support from any clinical data obtained with the spacer or holding chamber. See also Regional Information Appendix III: Devices, Spacers and Holding Chambers (European Union only).

4.2.1.7 Single dose fine particle mass (CTD 3.2.P.2.4)

The fine particle mass should be routinely determined using the minimum recommended dose, if technically possible. 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. Justification for not conducting this test (e.g., for low dosed products) and for non-equivalent results should be provided.

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. The selection of the pooled stages should be justified. 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.

4.2.1.8 Particle / droplet size distribution (CTD 3.2.P.2.4)

To allow an assessment of the complete profile of the product used in *in vivo* (pivotal clinical and/or comparative) 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 uni-modal log-normal distribution). Mass balance reconciliation should also be considered.

When a range of different strengths is proposed, proportionality in fine particle mass and other size ranges (e.g., mass deposited in the impactor throat) should be considered.

For solutions for nebulisation, droplet size distribution may be tested by other methods (e.g., laser diffraction).

4.2.1.9 Actuator / Mouthpiece deposition (CTD 3.2.P.2.4)

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

4.2.1.10 Drug delivery rate and total drug delivered (CTD 3.2.P.2.4)

To allow an assessment of the complete delivery profile of the product used in *in vivo* (pivotal clinical and/or comparative) studies, the drug delivery rate and total drug delivered (i.e. total dose delivered to the patient) results should be provided for the batches used in these studies. A validated method (e.g., breath simulator), should be employed. The aerosol should be generated with the nebuliser system(s) and settings used in the *in vivo* studies.

4.2.1.11 Shaking requirements (CTD 3.2.P.2.4)

For products requiring shaking before use (according to the instructions for 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.

4.2.1.12 Initial priming of the container (CTD 3.2.P.2.4)

A study should be conducted to support the number of actuations recommended in the labelling 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.

4.2.1.13 Re-priming of the container (CTD 3.2.P.2.4)

A study should be conducted to support the length of time that the product may be stored without use (after initial priming) before re-priming as recommended in the labelling, 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 need to test products at different stages through container life should also be considered. 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 be determined.

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

4.2.1.14 Cleaning requirements (CTD 3.2.P.2.4)

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.

4.2.1.15 Low temperature performance (CTD 3.2.P.2.4)

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 according to the instructions for use), 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. Alternative approaches for inhalation products which do not tolerate low temperatures should be fully justified.

4.2.1.16 Performance after temperature cycling (CTD 3.2.P.2.4)

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 suspensions, cycling between the recommended storage conditions and a high temperature (e.g., 40°C) should be considered, and may be combined with the low temperature cycling study. 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.

4.2.1.17 Effect of environmental moisture (CTD 3.2.P.2.4)

The effect of environmental 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.

4.2.1.18 Robustness (CTD 3.2.P.2.4)

The product performance should be investigated under conditions to simulate use by patients. This includes activating the delivery device at the frequency indicated in the instructions for use. Carrying the delivery device between use and simulation of dropping the delivery device, etc., and the robustness of any lockout mechanism should be considered.

Vibrational stability of powder mixtures should be demonstrated, in order to simulate vibrations during transport and 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.

4.2.1.19 Delivery device development (CTD 3.2.P.2.4 and 3.2.R)

The development of the delivery device should be described. Any changes implemented in the design (e.g., change of component materials) and/or manufacturing process of the delivery 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 delivery devices were used in clinical studies, appropriate 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 delivery devices, data should be provided to demonstrate that all target patient groups are capable of triggering the delivery 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 delivery device development programme.

For device-metered dry powder inhalers 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.

4.2.1.20 Preservative effectiveness / efficacy (CTD 3.2.P.2.5)

For products containing a preservative, a study should be conducted to demonstrate the effectiveness / efficacy of the preservative.

4.2.1.21 Compatibility (CTD 3.2.P.2.6)

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.

4.2.2 Nasal Products

The tests indicated in Table 4.2.2 are normally conducted to characterise nasal products. Not all tests are necessary for all types of nasal products, as noted in Table 4.2.2

The pharmaceutical development studies should be performed as discussed in Section 3.1, with the exception of tests for fine particle mass.

With regard to particle / droplet 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 (i.e., by demonstrating that the vast majority of the particles / droplets are larger than 10 microns).

Table 4.2.2 Pharmaceutical Development Studies for Nasal Products

Pharmaceutical Development Study	Pressurised Metered Dose Nasal Sprays	Nasal Powders (Device-Metered)	Nasal Liquids			
			Single Use Drops	Multiple Use Drops	Single Use Sprays	Non-Pressurised Multiple Use Metered Dose Sprays
(a) Physical characterisation	Yes*	Yes	Yes*	Yes*	Yes*	Yes*
(b) Minimum fill justification	Yes	Yes	Yes	Yes	Yes	Yes

Table 4.2.2 Pharmaceutical Development Studies for Nasal Products

Pharmaceutical Development Study	Pressurised Metered Dose Nasal Sprays	Nasal Powders (Device-Metered)	Nasal Liquids			
			Single Use Drops	Multiple Use Drops	Single Use Sprays	Non-Pressurised Multiple Use Metered Dose Sprays
(c) Extractables / Leachables	Yes	No	Yes	Yes	Yes	Yes
(d) Delivered dose uniformity through container life	Yes	Yes	No	No	No	Yes
(h) Particle / droplet size distribution	Yes	Yes	No	No	Yes	Yes
(i) Actuator / mouthpiece deposition	Yes	Yes	No	No	Yes	Yes
(k) Shaking requirements	Yes*	No	Yes*	Yes*	Yes*	Yes*
(l, m) Initial & re-priming requirements	Yes	No	No	No	Yes	Yes
(n) Cleaning requirements	Yes	Yes	No	Yes	No	Yes
(o) Low temperature performance	Yes	No	No	No	No	No
(p) Performance after temperature cycling	Yes	No	No	No	Yes	Yes
(q) Effect of environmental moisture	Yes	Yes	No	No	No	No
(r) Robustness	Yes	Yes	Yes	Yes	Yes	Yes
(s) Delivery device development	Yes	Yes	Yes	Yes	Yes	Yes

Table 4.2.2 Pharmaceutical Development Studies for Nasal Products

Pharmaceutical Development Study	Pressurised Metered Dose Nasal Sprays	Nasal Powders (Device-Metered)	Nasal Liquids			
			Single Use Drops	Multiple Use Drops	Single Use Sprays	Non-Pressurised Multiple Use Metered Dose Sprays
(t) Preservative effectiveness / efficacy	No	No	Yes**	Yes**	Yes**	Yes**

* For suspensions.

** If a preservative is present.

4.3 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).

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.

4.4 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) 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), it may be necessary to limit the source to a single, validated supplier. Alternatively, the suitability of different suppliers may 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 microbiological quality should be considered, and where applicable, justification provided for not conducting routine microbiological quality control tests.

4.4.1 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.

4.4.2 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.

4.5 DRUG PRODUCT SPECIFICATION(S)

This section describes specification tests specific to inhalation and nasal products. Standard drug product specification tests (e.g., identification, degradation products, pH) have not been included here, but it is expected that these tests be included in the specifications. Other guidance documents (e.g., ICH) should be consulted in this regard.

Acceptance criteria should be set based on the observed ranges of variation in batches that showed acceptable performance *in vivo*, as well as the intended use of the product. Process capability and stability data may also be considered. In addition, different tests and limits may apply at release versus shelf life; differences should be clearly described and justified. Other guidance documents that apply to all types of dosage forms should be consulted regarding specification-setting, release versus shelf-life testing, periodic testing, etc.

4.5.1 Inhalation Products

The following list includes the tests normally included in the drug product specifications for inhalation products. Not all tests are necessary for all types of inhalation products, as noted in Table 4.5.1.

Table 4.5.1: Drug Product Specification Tests for Inhalation Products

Drug Product Specification Test	Pressurised Metered Dose Inhalers	Dry Powder Inhalers		Products for Nebulisation		Non-Pressurised Metered Dose Inhalers
		Device-Metered	Pre-Metered	Single Dose	Multi-Dose	
(a) Description	Yes	Yes	Yes	Yes	Yes	Yes
(b) Assay	Yes	Yes	Yes	Yes	Yes	Yes
(c) Moisture content	Yes	Yes	Yes	No	No	No
(d) Mean delivered dose	Yes	Yes	Yes	No	No	Yes
(e) Delivered dose uniformity	Yes	Yes	Yes	No	No	Yes
(f) Content uniformity / Uniformity of dosage units	No	No	No	Yes	No	No
(g) Fine particle mass	Yes	Yes	Yes	Yes*	Yes*	Yes
(h) Leak rate	Yes	No	No	No	No	No
(i) Microbial / microbiological limits	Yes	Yes	Yes	Yes***	Yes	Yes
(j) Sterility	No	No	No	Yes**	No	No
(k) Leachables	Yes	No	No	Yes	Yes	Yes
(l) Preservative content	No	No	No	Yes***	Yes***	Yes***
(m) Number of actuations per container	Yes	Yes	No	No	No	Yes

* For suspensions.

** If the product is sterile.

*** If a preservative is present.

4.5.1.1 Description

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

4.5.1.2 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.

4.5.1.3 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.

4.5.1.4 Mean Delivered Dose

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

4.5.1.5 Delivered Dose Uniformity

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

The use of uniformity of weight per actuation in lieu of the uniformity of the content of the delivered dose may be acceptable for solution formulations. Justification should be provided.

4.5.1.6 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 uniformity of weight per actuation in lieu of content uniformity may be acceptable for solution formulations. Justification should be provided.

4.5.1.7 Fine Particle Mass

The fine particle mass test should be conducted using a validated multistage impactor or impinger method, or a suitably validated alternative. 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) studies and should be reported on a per actuation or per dose basis.

4.5.1.8 Leak Rate

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

4.5.1.9 Microbial / Microbiological Limits

Microbiological quality testing should be conducted according to an accepted pharmacopoeial test, or justification for not including this test should be including in the Justification of Specification(s) section.

4.5.1.10 Sterility

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

4.5.1.11 Leachables

Depending on the results of the pharmaceutical development study on extractables and leachables, and in particular the results of safety assessments (see Section 4.2.1.3 Drug Product Pharmaceutical Development: Inhalation Products), a test and qualified limits for leachables should be included in the specification.

4.5.1.12 Preservative content

Preservative assay testing should be conducted.

4.5.1.13 Number of actuations per container

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

4.5.2 Nasal Products

The following list includes the tests normally included in the drug product specifications for nasal products. Not all tests are necessary for all types of nasal products, as noted in Table 4.2.2.

The tests should be performed as discussed in Section 4.2.1, supplemented by a test for particle / droplet size distribution, if applicable. See below.

4.5.2.1 Particle / Droplet Size Distribution

Testing should be conducted using a validated method (e.g., cascade impaction or, for solutions, laser diffraction). The limits should include an allowed range for the median diameter and a limit on the sub 10 micron particles / droplets. The limits for the median diameter and the sub 10 micron particles / droplets should be qualified by results for batches used in in vivo (pivotal clinical and/or comparative) studies.

Table 4.5.2.1: Drug Product Specification Tests for Nasal Products

Drug Product Specification Test	Pressurised Metered Dose Nasal Sprays	Nasal Powders (Device-Metered)	Nasal Liquids			
			Single Use Drops	Multiple Use Drops	Single Use Sprays	Non-Pressurised Multiple Use Metered Dose Sprays
(a) Description	Yes	Yes	Yes	Yes	Yes	Yes
(b) Assay	Yes	Yes	Yes	Yes	Yes	Yes
(c) Moisture content	Yes	Yes	No	No	No	No
(d) Mean delivered dose	Yes	Yes	No	Yes	No	Yes
(e) Delivered dose uniformity	Yes	Yes	No	Yes	No	Yes
(f) Content uniformity / Uniformity of dosage units	No	No	Yes	No	Yes	No
(h) Leak rate	Yes	No	No	No	No	No
(i) Microbial / Microbiological limits	Yes	Yes	Yes**	Yes	Yes**	Yes
(j) Sterility	No	No	Yes*	Yes*	Yes*	Yes*
(l) Preservative content	No	No	Yes**	Yes**	Yes**	Yes**
(m) Number of actuations per container	Yes	Yes	No	No	No	Yes
(n) Particle / droplet size distribution	Yes	Yes	No	No	Yes	Yes

* If the product is sterile.

** If a preservative is present.

4.6 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 by the delivery device, where applicable. 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 (e.g., pharmacopoeial) 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 non-compendial components, in addition to the resin used, any additives included should also be described.

4.7 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. Weight loss should also be monitored where appropriate.

If product performance is considered to be influenced by the storage orientation (e.g., for pressurised metered dose inhalers), 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. For example, if a product should be used within three months after removal of the protective packaging (according to the instructions for use), the product should be removed from the protective packaging three months before the end of the shelf life, and tested at the end of the shelf life.

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

DEFINITIONS

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).
container closure system:	the sum of packaging components that together contain and protect the dosage form. The container closure system may serve as a delivery device.
delivered dose:	the quantity of drug substance that is available to the user, ex-device, on a per dose basis.
delivery device:	the sum of component(s) of the container closure system 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. One dose may consist of several actuations.
dosing interval:	the recommended length of time between doses, as specified in the information provided to consumers and health care professionals.
dry powder inhaler, device-metered:	an inhalation product containing a reservoir of powder which is measured into individual actuations by the delivery device.
dry powder inhaler, pre-metered:	an inhalation product containing pre-measured actuations, usually 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 stressful conditions.
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 or per dose basis.
geometric 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 delivery device, where applicable) whose intended site of deposition is the respiratory tract. The site of action may be local or systemic.

label claim:	the amount of drug (usually on a per actuation basis) declared on the label of the product.
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 delivery device metering chamber
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%.
minimum delivered dose:	the smallest recommended dose according to the Information for Consumers and Health Care Professionals, expressed as delivered dose.
nasal product:	a drug product (including the delivery device, where applicable) whose intended site of deposition is the nasal and/or pharyngeal region. The site of action may be local or systemic.
nebuliser:	a device used to continuously atomize liquids for inhalation.
non-pressurised metered dose inhaler:	portable, inhalation delivery device containing an aqueous solution, suspension or emulsion, which delivers one dose in one (or more) actuation(s).
non-pressurised metered dose nasal spray:	portable, nasal delivery device containing an aqueous solution, suspension or emulsion, which delivers one dose in one (or more) actuation(s).
pressurised metered dose inhaler:	an inhalation product containing one or more propellants in a pressurised delivery device.
pressurised metered dose nasal spray:	product for nasal administration containing one or more propellants in a pressurised delivery device.
product for nebulisation:	a liquid inhalation product administered via a commercially marketed nebuliser.
spray:	see actuation.
target delivered dose:	the quantity of drug substance expected to be released from the device in the number of actuations equivalent to a dose.
target delivery amount:	the quantity of drug substance expected to be released from the delivery device (i.e., ex-actuator or ex-device) in one actuation.
therapeutic index:	the ratio of the dose resulting in toxicity to the dose required to achieve the desired therapeutic effect.

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.(c) 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.(e) 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.(h) Particle / droplet 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.(j) Drug delivery rate and total drug delivered

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.

**APPENDIX II:
INFORMATION FOR CONSUMERS AND HEALTH CARE PROFESSIONALS
(SUMMARY OF PRODUCT CHARACTERISTICS)**

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, drug delivery rate and total drug delivered.

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 labelled claim is expressed as metered dose (ex valve) or as delivered dose (ex actuator).

Nasal Drops should be labelled 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.'

APPENDIX III: DEVICES INCLUDING SPACERS AND HOLDING CHAMBERS

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.