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Guideline on the pharmaceutical quality of inhalation and nasal medicinal products

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This guideline replaces the guideline on pharmaceutical quality of inhalation and nasal products (EMA/CHMP/QWP/49313/2005 Corr) and Quality of medicines questions and answers: Part 2 Specific type of products – Dry product inhalers; Orally inhaled products; Storage – What are the requirements for storage orientation recommendations in the product information for pressurised metered dose inhalers.

Keywords	Inhalation medicinal products, nasal medicinal products, pharmaceutical quality, pressurised metered-dose inhalers (pMDI), dry powder inhalers (DPI), medicinal products for nebulisation, non-pressurised metered-dose inhalers, nasal sprays, nasal powders, nasal liquids
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Guideline on the pharmaceutical quality of inhalation and nasal medicinal products

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Executive summary

This guideline is the first revision of the guideline on pharmaceutical quality of inhalation and nasal products (EMA/CHMP/QWP/49313/2005 Corr). The main aim of the first revision is to consolidate the information available in the previous guidance documents, the related published questions and answers, also taking into consideration recent advancements in the field, common practice and new regulations, including the medical device regulation. Requirements for demonstration of therapeutic equivalence for orally inhaled products (OIP) are included in the Guideline on the requirements for demonstrating therapeutic equivalence between orally inhaled products (OIP) for asthma and chronic obstructive pulmonary disease (COPD). These two guidelines are complementary and should be read in conjunction to each other.

1. Introduction (background)

This guideline concerns the quality aspects of human medicinal products intended for delivery of active substance(s) into the lungs or to the nasal mucosa with the purpose of evoking a local or systemic effect, including effects in the central nervous system (CNS), achieved through the nose-to-brain route. Quality aspects specific to inhalation and nasal medicinal products are discussed, the need for safety testing (e.g., for excipients and leachables) is also considered. 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 primarily used for inhalation and nasal medicinal products (e.g., cascade impactor analysis) is not included in this guideline. This information may be found in other publications (e.g., European Pharmacopoeia).

2. Scope

The guideline addresses requirements "on the quality of inhalation and nasal medicinal products" in new marketing authorisation applications, including abridged applications. The general principles described in this guideline should also be considered when making changes to authorised medicinal products and during development of medicinal 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 active substance and finished medicinal product batches used in pivotal clinical trials is necessary to qualify the medicinal product proposed for marketing.

This guideline has been developed for medicinal products containing active substances of synthetic or semi-synthetic origin. However, the general principles described should also be considered for other inhalation and nasal medicinal products with active substances of other origins.

The guideline applies to medicinal products developed for administration of active substance(s) to the lungs, such as pressurised and non-pressurised metered-dose inhalers (MDI), dry powder inhalers (DPI), medicinal products for nebulisation, as well as pressurised metered-dose nasal sprays, nasal powders and nasal liquids. Liquid inhalation anaesthetics and nasal ointments, creams and gels are excluded, however the general principles described in this guideline should be considered.

3. Legal basis and relevant guidelines

This guideline should be read in conjunction with the introduction and general principles of Annex I to Directive 2001/83/EC, as amended, and all other relevant EU and ICH guidelines. These include, but are not limited to:

- Regulation (EU) 2017/745 on Medical Devices,
- Guideline on the requirements for demonstrating therapeutic equivalence between orally inhaled products (OIP) for asthma and chronic obstructive pulmonary disease (COPD) (CPMP/EWP/4151/00 Rev. 2),
- Guideline on quality documentation for medicinal products when used with a medical device (EMA/CHMP/QWP/BWP/259165/2019) and the related Q&As on the implementation of the Medical Device Regulation,
- Questions and answers on data requirements when transitioning to low global warming potential (LGWP) propellants in oral pressurised metered dose inhalers (EMA/CHMP/83033/2023 Corr.1),
- European Pharmacopeia.

4. Inhalation medicinal products

4.1. Active substance (S)

For all inhalation finished medicinal products containing an active substance that is not dissolved at any time during the finished product manufacture, storage or use, the particle size of that active substance is a critical parameter. A complete description of the particle-size adjustment process (e.g., jet-milling or spray-drying as micronisation process) and the in-process controls should be provided. Sufficient details need to be included in the active substance section (S) and referenced in pharmaceutical development section (P.2), to assure the required quality of the micronised active substance.

The active substance specification should include a test for particle size and specified acceptance criteria. A validated particle sizing method (e.g., laser diffraction), with acceptance criteria set at multiple points across the particle 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* (i.e., pivotal clinical batches and/or batches used in pivotal pharmacokinetic studies), or *in vitro* comparative studies. Process capability may also be considered.

Other relevant characteristics of the active substance should also be considered. For example, different polymorphic forms including any amorphous content could affect the quality or performance of the finished medicinal product. If relevant, the appropriate solid-state form should be specified and controlled in accordance with ICH Q6A.

Control of microbiological quality should be considered where applicable.

If alternative suppliers of the active substance are proposed, one single compiled specification should be applied, supported by appropriate physical characterisation and *in vitro* performance studies (see section 4.2.2 Pharmaceutical Development).

4.2. Finished medicinal product (P)

4.2.1. Description and composition of the finished medicinal product (P.1)

The complete qualitative and quantitative composition should be specified including excipients and any other components (e.g., solvents, gasses) removed during manufacturing. The amount of each active substance and excipient should be expressed in concentration (i.e., amount per unit volume or weight) and total amount per container. Amount per actuation of each active substance should be defined both as metered and delivered dose. It is recommended to state the calculated amount of each excipient per actuation as metered and delivered dose as well.

The primary packaging, type of inhaler and, if necessary, the secondary packaging or other components required, for example, for additional protection (e.g., from environmental conditions, transportation) should be described.

4.2.2. Pharmaceutical development (P.2)

Pharmaceutical development studies are conducted to demonstrate that the formulation, pharmaceutical form, manufacturing process, delivery device, container closure system, and microbiological attributes are appropriate and result in acceptable product performance for the target patient population. The development should ensure that the labelled delivered dose is administered in a reproducible and accurate manner. The pharmaceutical development should include relevant usability studies to cover how the finished medicinal product should be used.

Quality by design (QbD) may be used as a development tool. A suitable design of experiments (DoE) should be chosen in relation to the development stage. In the late development stage, studies should be conducted on more than one batch, to account for both *inter* and *intra* batch variability; it is recommended to include a minimum of three batches with at least ten inhalers or units from each batch. The batches used for the pharmaceutical development should be representative of the commercial medicinal product; however, pilot scale batches may be acceptable. In the case of multiple strengths, multiple package sizes or other variables (e.g., number of doses in each inhaler, storage orientations), a justified bracketing and/or matrixing design may be used. The use of different batches of active substance, excipients and devices (components) should be considered, if relevant.

Sufficient data should be provided to adequately investigate all performance characteristics, independently of whether they may not be routinely tested (e.g., priming and testing to exhaustion). All batches that showed acceptable performance *in vivo* (i.e., pivotal clinical batches and/or batches used in pivotal pharmacokinetic studies), or *in vitro* comparative studies, should be sufficiently characterised to support the specification for the finished medicinal product.

The tests indicated in Table 4.2.1 are normally conducted to characterise inhalation medicinal products. Not all tests are necessary for all types of inhalation medicinal products. If the tests described are not conducted due to the particular nature of the finished medicinal product or because assurance of the parameter has been established by other means, a justification for the omission should be provided. Any of the development tests may be applicable to any pharmaceutical form, depending on the instructions for use in the package leaflet (e.g., shaking tests for certain DPI). Moreover, depending on the operational characteristics of the delivery device, additional studies relevant to the performance of the finished medicinal product may be necessary.

Table 4.2.1. Pharmaceutical development studies for inhalation medicinal products.

Pharmaceutical development study	Pressurised metered-dose inhalers (pMDI)	Dry powder inhalers (DPI)		Preparations for nebulisation		Non-pressurised metered-dose inhalers
		Device-metered	Pre-metered	Single-dose	Multi-dose	
(a) Physical characterisation	Yes ^a	Yes	Yes	Yes ^a	Yes ^a	Yes ^a
(b) Minimum fill justification	Yes	Yes	Yes	Yes	Yes	Yes
(c) Extractable volume	No	No	No	Yes	No	No
(d) Extractables / leachables	Yes	No	No	Yes	Yes	Yes
(e) Single-dose fine particle dose	Yes	Yes	Yes	No	No	Yes
(f) Aerodynamic particle / droplet size distribution	Yes	Yes	Yes	Yes	Yes	Yes
(g) Uniformity of delivered dose and fine particle dose through container life	Yes	Yes	Yes	No	Yes ^a	Yes
(h) Uniformity of delivered dose and fine particle dose over patient flow rate range	No	Yes	Yes	No	No	No
(i) Aerodynamic particle size distribution with spacer use	Yes	No	No	No	No	No
(j) Actuator / mouthpiece deposition	Yes	Yes	Yes	No	No	Yes
(k) Delivery rate and total delivered dose	No	No	No	Yes	Yes	No
(l) Shaking requirements	Yes ^a	No	No	Yes ^a	Yes ^a	Yes ^a
(m,n) Initial & re-priming requirements	Yes	No	No	No	No	Yes
(o) Cleaning requirements	Yes	Yes	Yes	No	Yes ^b	Yes
(p) Low temperature performance	Yes	No	No	No	No	No
(q) Performance and physical characterisation after temperature cycling	Yes	Yes	Yes	Yes	Yes	Yes
(r) Effect of environmental moisture	Yes	Yes	Yes	No	No	No
(s) Robustness	Yes	Yes	Yes	No	No	Yes
(t) Delivery device development	Yes	Yes	Yes	Yes	Yes	Yes
(u) Preservative effectiveness / efficacy	No	No	No	Yes ^c	Yes ^c	Yes ^c
(v) Compatibility	No	No	No	Yes	Yes	No
(x) Spray pattern / plume geometry	Yes	No	No	No	No	Yes

^aFor suspensions.^bFor co-packed medical device.^cIf a preservative is present.**4.2.2.1. (a) Physical characterisation (P.2.1.1 and P.2.1.2)**

Physical characteristics of the active substance(s) and excipients, such as solubility, particle size, particle shape, density, rugosity, charge, polymorphic form and crystallinity may influence the homogeneity, reproducibility and performance of the finished medicinal product. Development studies

should include the physical characterisation of the active substance(s) and excipients relevant to their effect on the performance of the finished medicinal product.

If applicable, the effect of pre-processing (e.g., micronisation) active substance(s) and/or excipient(s) on the physical properties should be evaluated and reported, including storage conditions and time for conditioning of the ingredients. Relevant information on the development of the pre-processing steps should be included.

For the finished medicinal product, development and characterisation studies based on dissolution testing can be provided as supportive information.

4.2.2.2. (b) Minimum fill justification (P.2.2.2)

For MDIs and device-metered DPIs, a study should be conducted to demonstrate that the individual container minimum fill, as defined by the finished medicinal product manufacturing process, is sufficient to provide the number of actuations stated in the product information. The last doses delivered by the inhaler as defined by the label claim, should meet the finished medicinal product specification limits for delivered dose and fine particle dose.

For pre-metered DPI and medicinal products for nebulisation, the fill volume and/or weight should be justified by demonstrating acceptable uniformity of delivered dose and fine particle dose throughout the defined fill volume range.

4.2.2.3. (c) Extractable volume (P.2.2.2)

The extractable volume may differ from the fill volume due to retaining of the finished medicinal product in the container closure system and may depend on the materials and shape/dimensions of the container.

4.2.2.4. (d) Extractables / leachables (P.2.4)

For compendial plastic materials a reference to the relevant European pharmacopoeial monograph, or the monograph of a member state should be provided. The leachables profile should be determined for plastic container closure components, in line with guidance.

For non-compendial plastic materials, rubber container closure components and any other relevant components that are in contact with the formulation during storage (e.g., valves and oil and lubricants used in the valve), a study should be conducted to determine the extractables profile even when the material is approved for use in food packaging. Details and justification of the study design (e.g., solvents used, temperature, storage time) substantiating its representativeness and the results should be provided. Leachables studies should be executed as appropriate, based on the results of the extractables studies. The principles described in relevant guidelines (e.g., CPMP/QWP/4359/03 Guideline on plastic immediate packaging materials, ICH Q3E and other applicable EMA/ICH guidelines) should be taken into account. 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 medicinal product or to when the equilibrium point is reached, if sooner.

Inhalation products present specific peculiarities when compared to other pharmaceutical forms; for example, the lack of animal/PK models, the scarcity of toxicological data, and the potential for sensitisation are factors to consider when designing extractable/leachable studies. The use of components potentially leaching compounds with structural alerts belonging to the cohort of concern should be avoided.

Depending on the levels and types of compounds detected, consideration should be given to include a test and limits for leachables in the finished medicinal product specification. If a correlation between extractable and leachable profiles can be established, control of leachables could be accomplished via testing and limits of extractables on the components.

4.2.2.5. (e) Single-dose fine particle dose (P.2.4)

The fine particle dose should be routinely determined using the minimum number of actuations in the recommended dose specified in the product information, if technically possible. If the fine particle dose test included in the finished medicinal product specification uses a number of actuations greater than the minimum number of actuations per dose, a study should be conducted to demonstrate that the sample size used routinely provides results comparable to those obtained using the minimum number of actuations. The method for fine particle dose in the finished medicinal product specification should be used, modified only as necessary to accommodate the reduced number of actuations. The amount deposited on each stage of the cascade impactor should be sufficient for a reliable assay, but not too excessive to bias the results by masking individual actuation variability. If this study is not feasible due to the sensitivity of the analytical method (e.g., for low dosed medicinal products), data supporting this claim should be provided.

4.2.2.6. (f) Aerodynamic particle / droplet size distribution (P.2.4)

The aerodynamic particle size distribution (APSD) is one of the Critical Quality Attributes (CQA) of inhalation medicinal products. It is therefore important to fully characterise the APSD during the development to ensure consistency with the commercial medicinal product.

To allow an assessment of the complete profile of the medicinal product that showed acceptable performance *in vivo* (i.e., pivotal clinical batches and/or batches used in pivotal pharmacokinetic studies), or *in vitro* 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. Any differences between the commercial and clinical batches should be explained and justified.

Using a multistage impactor or impinger, the mass of the active substance(s) on each stage and the cumulative mass undersize, at a given stage, should be determined instead of the percentage of the emitted dose 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. Mass balance reconciliation should also be considered.

When a range of different strengths is proposed, proportionality in APSD stages, or group of stages, should be determined and evaluated for clinical impact.

For solutions for nebulisation and water based non-pressurised MDI, droplet size distribution may be tested by other methods than cascade impactor (e.g., laser diffraction, if cross-validated against a cascade impaction method).

4.2.2.7. (g) Uniformity of delivered dose and fine particle dose through container life (P.2.4)

A study should be conducted to demonstrate the consistency of the delivered dose and the fine particle dose through the life of the container from the first dose (post-priming for products with priming instructions) until the last labelled dose. The study should be performed using the minimum recommended dose as stated in the product information (i.e., one or more actuations). The finished

product should be used and tested according to the instructions given in the package leaflet with respect to storage orientation and cleaning requirements, as well as the minimum dosing interval. For MDIs, pressurised and non-pressurised, and for device-metered DPI at least ten doses from the combination of the beginning, middle and end of a single container should be tested. For pre-metered DPI ten doses should be tested.

The doses should meet the finished medicinal product specification limits for uniformity of delivered dose and fine particle dose. Non-conforming results should be explained.

The doses between the last labelled dose and the last container exhaustion dose should also be tested and information on the tail-off profile should be provided where applicable. This testing may be waived if the container contains a lockout mechanism that prevents dosing beyond the labelled number of doses.

4.2.2.8. (h) Uniformity of delivered dose and fine particle dose over patient flow rate range (P.2.4)

A study should be conducted to demonstrate the consistency of the delivered dose and the fine particle dose over a range of flow rates (through the delivery device) covering the inspiratory ability of the intended patient population. Using three fixed flow rates in a range of about 30-90 L/min is typically acceptable, or flow rates corresponding to a pressure drop in a range of about 2-6 kPa.

4.2.2.9. (i) Aerodynamic particle size distribution and delivered dose with spacer / holding chamber use (P.2.4)

For inhalation medicinal products that may be administered with a spacer or holding chamber, studies should be conducted to determine to what extent the use of the spacer or holding chamber changes the aerodynamic particle size distribution (APSD) and the delivered dose. If the instructions accompanying the spacer or holding chamber include an in-use cleaning schedule (e.g., weekly cleaning), the APSD should be tested before and after cleaning the spacer or holding chamber according to the instructions provided with the delivery device. Differences in APSD when using spacer or holding chamber could impact the therapeutic equivalence, hence clinical studies might be needed (CPMP/EWP/4151/00 Rev. 2 Guideline on the requirements for demonstrating therapeutic equivalence between orally inhaled products (OIP) for asthma and chronic obstructive pulmonary disease (COPD)).

The testing of APSD and delivered dose may be altered, to mimic patient performance with the spacer or holding chamber (e.g., a two seconds delay for APSD by a multistage cascade impactor, tidal breathing for delivered dose). To reduce variability, the potential impact of external factors should be taken into considerations. As an example, special precautions such as earthing of the spacer and handling of the test equipment may be considered for minimising the impact of electrostatic interference.

4.2.2.10. (j) Actuator / mouthpiece deposition (P.2.4)

The amount of active substance(s) 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.

4.2.2.11. (k) Delivery rate and total delivered dose (P.2.4)

To allow an assessment of the complete delivery profile of the medicinal product used for *in vivo* studies (i.e., pivotal clinical batches and/or batches used in pivotal pharmacokinetic studies) or *in vitro* comparative studies, the active substance(s) delivery rate and total active substance delivered should

be provided. 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 or comparative *in vitro* studies.

4.2.2.12. (l) Shaking requirements (P.2.4)

For finished medicinal products that according to the instructions given in the package leaflet, require shaking before use, a study should be conducted to demonstrate that the shaking instructions are adequate. The possibility of shaking leading to inaccurate dosing (e.g., due to foaming) or other changes in product performance, should be examined by testing the delivered dose uniformity.

4.2.2.13. (m) Initial priming of the container (P.2.4)

A study should be conducted to support the number of actuations that should be fired to waste (priming actuations) prior to the patient using the medicinal product for the first time. Containers should be stored in various orientations prior to the initiation of the study in order to account for the different storage orientations likely to occur in real life settings. The length of storage prior to conducting the study should be indicated and justified. If storage orientation has a significant effect on the delivered dose a storage orientation recommendation should be added in the product information.

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

Priming instructions should be provided in the product information.

4.2.2.14. (n) Re-priming of the container following storage (P.2.4)

A study should be conducted to support the length of time that the finished medicinal product may be stored without being used (after initial priming) before re-priming is needed. Multiple time points should be investigated, and 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. The number of re-priming actuations required until the subsequent doses meet the finished medicinal product specification limits for delivered dose uniformity should be determined.

Re-priming instructions, including the length of storage after which re-priming should be performed, the number of re-priming actuations required and any necessary instructions with respect to storage orientation, should be provided in the product information. The instructions must be confirmed by user-acceptance testing. As it cannot be guaranteed that the medicinal product is always stored in the preferred orientation, the re-priming instructions should be based on the worst-case scenario (i.e., the orientation which requires the shortest re-priming period and/or the highest number of re-priming actuations).

4.2.2.15. (o) Cleaning requirements (P.2.4)

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

If the delivery device is designed to have the mouthpiece removed for periodic cleaning, testing should be performed in accordance with the instructions given in the product information, and as a worst case without removal and cleaning.

4.2.2.16. (p) Low temperature performance (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 finished medicinal product specification limits for delivered dose uniformity and fine particle dose 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.

If needed, instructions regarding cold temperature use should be provided in the product information, as supported by data.

4.2.2.17. (q) Performance and physical characterisation after temperature cycling (P.2.4)

The effect of temperature cycling on the performance of the product should be evaluated. A study should be conducted for 3-4 weeks using containers stored in various orientations and cycled between one temperature below freezing (-10 to -20°C) and one above room temperature (40°C). Storage time should be at least 12 hours under each condition. Alternative conditions and durations can be used, if justified.

The containers should be examined visually for any obvious defects, and tests such as leak rate, weight loss, delivered dose uniformity, fine particle dose, degradation products and moisture content should be performed. Any changes from initial results should be assessed for their significance. For DPIs, relevant physical characterisation should be performed (see section 4.2.2.1).

4.2.2.18. (r) Effect of environmental moisture (P.2.4)

The effect of environmental moisture on product performance of unprotected finished medicinal product (e.g., without protecting pouch) should be investigated during development. The propellant in pMDIs may have a high affinity for water. The APSD of DPIs may be impacted by moisture. In view of the potential impact of environmental moisture and temperature on the performance of the finished medicinal product, studies at 25°C/70% RH, or higher humidity, are expected. For pre-metered products using capsules, special attention should be given to brittleness of the capsules under various humidity conditions, and therefore, studies at lower humidity (e.g., 35% RH or 40% RH) are also expected.

4.2.2.19. (s) Robustness (P.2.4)

The product performance should be investigated under conditions intended to simulate patient use. This includes activating the delivery device at the frequency indicated in the product information. Carrying the delivery device between use, simulation of dropping the delivery device and the robustness of any lockout mechanism, digital sensor etc., 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 dose should be fully discussed in terms of the safety and efficacy of the medicinal product.

Dropping of the delivery device should be investigated. The dropping simulation should be performed towards the end of the life of the product (e.g., at dose 180 for a 200 doses product) in order to assess the effect of finished medicinal product accumulated on the mouthpiece, or any other part of the

delivery device, during the life-time of the delivery device. Significant variations in the delivered dose and/or fine particle dose should be discussed in terms of the safety and efficacy of the medicinal product. Appropriate handling instructions should be established based on the results obtained and included in the product information.

4.2.2.20. (t) Delivery device development (P.2.4 and 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 medicinal product should be discussed in terms of the impact on the product performance characteristics (e.g., delivered dose, fine particle dose). If prototype delivery devices were used in clinical studies, their equivalence with the delivery device intended for marketing should be demonstrated by providing equivalence performance data as described in section 5 in the Guideline on the requirements for demonstrating therapeutic equivalence between orally inhaled products (OIP) for asthma and chronic obstructive pulmonary disease (COPD) (CPMP/EWP/4151/00 Rev. 2).

For DPI, safeguards to prevent inadvertent multiple dose metering (and subsequent inhalation by the patient) should be demonstrated.

For breath-actuated delivery devices, data should be provided to demonstrate that the target patient groups are capable of triggering the delivery device. Unless this aspect is covered by clinical data, dedicated patient usability studies may be warranted. The triggering mechanism should be well characterised as part of the delivery device development programme.

The number of doses used and/or remaining in multidose inhalation medicinal products is considered key information for the patient; hence, multidose inhalation medicinal products should be equipped with a dose counter. Alternatively, a different methodology can be applied and described in the product information, to determine the remaining life-time of the inhaler (e.g., dose indicator).

4.2.2.21. (u) Preservative effectiveness / efficacy (P.2.5)

For medicinal products containing a preservative, a study should be conducted to demonstrate the need and effectiveness/efficacy of the preservative. Minimum concentration of preservative should be used to give the required level of efficacy.

4.2.2.22. (v) Compatibility (P.2.6)

If the medicinal product is to be diluted prior to administration compatibility should be demonstrated with all diluents over the range of dilution proposed in the product information. These studies should preferably be conducted on aged samples and should cover the duration of storage of the diluted medicinal product indicated in the product information. Where the product information specifies co-administration with other medicinal products, compatibility with all the finished medicinal products should be demonstrated.

Parameters such as precipitation, pH, droplet size distribution, delivery rate and delivered dose should be tested and differences from the concentrated product should be assessed for their significance.

4.2.2.23. (x) Spray pattern / plume geometry (P.2.4)

Spray pattern and plume geometry should be studied where appropriate to characterise the performance of the complete finished medicinal product, i.e., the formulation in combination with the delivery device.

4.2.3. Manufacture (P.3)

A detailed description of the manufacturing process for the finished medicinal product, including filling and packaging, should be included. If the particle size of the active substance(s), or of any excipient, is controlled, the particle size adjustment process (e.g., micronisation) should be described. Any conditioning of DPIs or equilibration time allowed for pressurised medicinal products, before release testing, should be specified and justified along with other aspects of the manufacturing process.

Inhalation medicinal products are considered specialised dosage forms manufactured by non-standard manufacturing processes. P.3.3 and P.3.4 should be sufficiently detailed and include both critical and non-critical process parameters justified by the manufacturing process development undertaken.

The controls for critical steps and intermediates should be described. Appropriate in-process controls should be established based on the CQAs and Critical Process Parameters (CPPs) determined during the development studies, e.g., performance testing of the actuation release mechanism (shot weight) of each unit, homogeneity of the formulation.

The manufacturing process should be validated. The validation should cover product specific characteristics, for example, it should 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 inhalers, blister sealing for DPI). For integral drug device combination products, the yield of the final assembling step of the validation batches should be reported and discussed to ensure a robust process. The scale of manufacture should be supported by process validation batch data at the proposed production scale. Exemptions may be accepted if adequately justified as described in the guideline on process validation (EMA/CHMP/CVMP/QWP/BWP/70278/2012 Rev 1 Corr 1).

4.2.4. Control of excipients (P.4)

For most inhalation medicinal products, excipients (when used) comprise a significant part of the formulation content by weight and thereby may have a substantial effect on safety, quality and performance of the medicinal product. Besides pharmacopoeial requirements additional functionality-related tests should be included in the specifications as appropriate. For all excipients specifications should be set in consideration of their impact on the finished medicinal product CQAs, as justified during finished medicinal product development.

For DPI, a suitable multi-point particle size test should be included for the excipient(s) (e.g., lactose) or where appropriate for granules consisting of a mixture of excipients and/or the active substance(s). The limits for this test should be qualified by the results of batches used in the *in vivo* studies (i.e., pivotal clinical batches and/or batches used in pivotal pharmacokinetic studies), or *in vitro* comparative studies, although *in vitro* data (from multistage impaction/impinger) may suffice to demonstrate the suitability of the extremes of the limits. Process capability and other development data may also be considered.

Control of microbiological quality should be considered and, where applicable, justification provided for not conducting routine microbiological quality control tests.

Control of 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 finished medicinal product performance (e.g., morphology of particles, viscosity number), it may be necessary to limit the source to a single, validated, named supplier. Alternatively, the suitability of different suppliers may be demonstrated with *in vitro* data for finished medicinal product manufactured

with different batches from each source. If these conditions are met, the omission of the relevant specification criteria, other than particle size distribution (if relevant), can be justified based on data.

4.2.4.1. Pharmacopoeial excipients

Excipients that have a well-established history of use in inhalation medicinal 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 inhalation route of administration.

For any excipient without a well-established history of use in inhalation medicinal products or is used at a concentration above that previously used by the inhalation route, safety must be sufficiently demonstrated by providing relevant data in Module 4.

4.2.4.2. Non-pharmacopoeial excipients

For excipients not described in any pharmacopoeia appropriate specification tests and limits, particularly with respect to purity, should be established and justified. Justification is not required for well-known excipients which have been used in similar finished medicinal products for a long period of time.

Excipients that are not well-known must be demonstrated to be safe when administered by the inhalation route of administration, relevant data should be provided in Module 4. In addition, information on the manufacture of the excipient may also be necessary. A general outline of the manufacturing and purification procedures may be sufficient.

4.2.4.3. Novel excipients

For excipients that are not used in inhalation medicinal products before, full details of manufacture, characterisation and controls with cross reference to supporting safety data (provided in Module 4) should be provided. The documentation on chemistry should include the origin of the excipient, including the name and address of the supplier and a general outline of the manufacturing and purification procedures. The chemical structure, and if appropriate morphological information, should be included. Physical and chemical properties, identification and purity need to be tested by validated analytical methods. Batch results and stability data should be provided.

4.2.5. Control of the finished medicinal product (P.5)

This section describes specification tests specific to inhalation medicinal products. Standard finished medicinal product specification tests (e.g., identification, degradation products, pH) have not been listed, but it is expected that these tests are included in the specifications, as needed. Other guidance documents (e.g., ICH Q6A) should be consulted in this regard.

Acceptance criteria should be set based on the observed ranges of variability in batches used in the *in vivo* studies (i.e., pivotal clinical batches and/or batches used in pivotal pharmacokinetic studies), or *in vitro* comparative studies. Process capability may also be considered. In addition, different tests and limits may apply at release versus shelf-life; differences should be clearly described and justified.

Table 4.2.2 includes the tests normally included in the finished medicinal product specifications for inhalation medicinal products. Not all tests are necessary for all types of inhalation medicinal products, as noted in table. 4.2.2.

Table 4.2.2. Finished medicinal product specification tests for inhalation medicinal products.

Finished medicinal product specification test	Pressurised metered-dose inhalers (pMDI)	Dry powder inhalers (DPI)		Preparations 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) Uniformity of delivered dose	Yes	Yes	Yes	No	No	Yes
(f) Content uniformity / uniformity of dosage units	No	No	No	Yes	No	No
(g) Fine particle dose	Yes	Yes	Yes	Yes ^a	Yes ^a	Yes
(h) Leak rate	Yes	No	No	No	No	No
(i) Microbial / microbiological limits	Yes	Yes	Yes	Yes ^b	Yes	Yes
(j) Sterility	No	No	No	Yes ^c	Yes ^c	No
(k) Leachables	Yes	No	No	Yes	Yes	Yes
(l) Preservative content	No	No	No	Yes ^b	Yes ^b	Yes ^b
(m) Number of deliveries per container	Yes	Yes	No	No	No	Yes

^a For suspensions.

^b If a preservative is present.

^c If the product is sterile.

4.2.5.1. (a) Description

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

4.2.5.2. (b) Assay

For multidose medicinal products, the amount of the active substance(s) should be determined per weight unit or per volume unit, as applicable. For single-dose medicinal products, the assay should be expressed as mass per dosage unit. At release assay limits of $\pm 5\%$ should apply unless otherwise justified.

4.2.5.3. (c) Moisture content

The limit for moisture content should be established based on results in stability studies. If the results are stable throughout the shelf-life of the medicinal product, or if it has been demonstrated that 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.

4.2.5.4. (d) Mean delivered dose

The amount of active substance in one actuation should be determined by calculating the mean of the delivered dose uniformity test results (see 4.2.5.5), with corrections as necessary to convert from "per dose" amounts to "per actuation" amounts. Limits of $\pm 15\%$ of the label claim should apply, as stated in accepted pharmacopeia (e.g., Ph. Eur. monograph "Preparations for inhalation").

4.2.5.5. (e) Uniformity of delivered dose

Uniformity of delivered dose should be ensured both within a delivery device (*intra*-inhaler) and between delivery devices (*inter*-inhaler). For single-dose preparations, *intra*-inhaler test is not required. The tests should be conducted according to pharmacopoeial methods, or suitably validated alternatives. A single test combining *intra* and *inter* variability may be acceptable provided that the test method is suitably justified and validated.

Limits applied should be consistent with accepted pharmacopeia, with adaption as necessary to test both *intra* and *inter* delivery 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.

4.2.5.6. (f) Content uniformity / uniformity of dosage units

Content uniformity should be investigated on samples removed from the containers as per the instructions provided to patients and health care professionals. Acceptance limits should be justified, taking into consideration pharmacopoeial requirements.

The use of uniformity of weight in lieu of content uniformity may be acceptable for solution formulations.

4.2.5.7. (g) Fine particle dose

The fine particle dose test should be conducted using a validated multistage impactor or impinger method, or a suitably validated alternative (e.g., an abbreviated impactor method, AIM). If using an abbreviated impactor, cross-validation or verification between the full resolution impactor method and the abbreviated method needs to be performed. Where an abbreviated method is used for routine testing, results of batches used in the *in vivo* studies (i.e., pivotal clinical batches and/or batches used in pivotal pharmacokinetic studies), or *in vitro* comparative studies should be provided, using the same method.

It is normally considered acceptable and preferred to set upper and lower limits on the results of pooled stages corresponding to a particle size distribution of less than 5 µm as specified, for example, in Ph. Eur. 2.9.18. Alternative particle size limits may be found acceptable with adequate justification. The mass of the active substance(s) 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 dose 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 efficacy and safety of the medicinal product.

In all cases, limits should be qualified by the fine particle dose results for batches used for *in vivo* studies (i.e., pivotal clinical batches and/or batches used in pivotal pharmacokinetic studies), or *in vitro* comparative studies, and should be reported on a per actuation or per dose basis. Normally, it is considered that a specification range should not be wider than ±25% for adequate quality control of most inhalation medicinal products, based on the manufacturing process and the variability of the analytical methods. It should be taken into account that preferably the same analytical methods are used for the determination of fine particle dose of batches that were pivotal for the demonstration of efficacy and safety, as well as for the medicinal product intended for the market. The proposed specification limits should take into account the shelf-life performance of the medicinal product. If there are differences observed compared to the medicinal product at release, the clinical relevance should be discussed. A tighter specification limit at release may be required to ensure acceptable medicinal product performance at end of shelf-life.

If there are several strengths, the specification range(s) for each of the strengths should normally not overlap.

4.2.5.8. (h) Leak rate

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

4.2.5.9. (i) Microbial / microbiological limits

Microbiological quality testing should be conducted according to an accepted pharmacopoeial test, or justification for not including this test should be included.

4.2.5.10. (j) Sterility

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

4.2.5.11. (k) Leachables

Depending on the results of the pharmaceutical development study on extractables and leachables, and in particular the results of safety assessments (see section 4.2.2.4), a test and qualified limits for leachables should be included in the specification.

4.2.5.12. (l) Preservative content

Preservative assay testing should be conducted.

4.2.5.13. (m) Number of deliveries per container

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

4.2.6. Container closure system (P.7 and R)

In addition to standard container closure system specification tests (e.g., identification, dimensions), the specifications of the container closure system should include, where applicable, further tests to confirm reproducible delivery of the finished medicinal product by the delivery device. For example, for pMDI, specifications should include tests such as shot weight of individual sprays and actuator orifice length and diameter. In addition to the schematic drawings of the delivery device, pictures should also be provided.

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 multidose inhalation medicinal products the dose counter or other method to determine the remaining life-time of the inhaler should be described. For coated canisters and/or valves, the complete composition of the coating and the process (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.

All inhalation (and nasal) drug delivery devices, have to fulfil the general requirements as outlined in the Medical Device Regulation (EU) 2017/745. The delivery device shall meet the applicable general safety and performance requirements set out in Annex I of Regulation (EU) 2017/745, taking into

account its intended purpose. For delivery devices that are co-packaged with the medicinal product and that are non-integral drug device combination products, evidence should be provided that relevant standards have been met e.g., the dossier should include a discussion demonstrating that the GSPRs have been met, EU Declaration of Conformity or NB Certificate of Conformity, or other appropriate documentation. The dossier should include information related to demonstration of compliance of the delivery device with Annex I of Regulation (EU) 2017/745. Further requirements are outlined in EMA/CHMP/QWP/BWP/259165/2019 "Guideline on the quality requirements for drug device combination products".

4.2.7. Stability (P.8)

All inhalation medicinal products should be tested on stability against the stability indicating tests included in the finished medicinal product specification. Weight loss should also be monitored where appropriate.

If product performance is considered to be influenced by the storage orientation (e.g., for pMDI), 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 medicinal product includes secondary packaging in order to protect it from environmental conditions, such as, light and/or moisture (e.g., DPI inside a foil overwrap), the length of time that the medicinal product may be used after the protective packaging has been removed should be supported by an in-use stability study. These in-use studies should involve removing the medicinal product from the protective packaging close to the end of its shelf-life and testing the exposed medicinal product against the finished medicinal product specifications. For example, if a medicinal product should be used within three months after removal of the protective packaging (according to the instructions for use), the medicinal 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 medicinal product once the protective packaging has been removed should be provided to the patient.

4.3. Therapeutic equivalence

The quality requirements to be considered for the development of a medicinal product which is intended to be authorised by an abridged application are not different from the development of the inhalation medicinal product used as a reference medicinal product. Quality data requirements as described in this guideline should be met, supplemented by appropriate comparative quality and clinical data with respect to the chosen reference medicinal product.

For inhalation medicinal products comparative *in vitro* data between the abridged application medicinal product and the reference medicinal product must be provided. The pharmaceutical criteria for demonstrating therapeutic equivalence as described in Guideline on the requirements for demonstrating therapeutic equivalence between orally inhaled products (OIP) for asthma and chronic obstructive pulmonary disease (COPD) (CPMP/EWP/4151/00 Rev. 2) may be considered even for medicinal products with different indications.

If no *in vivo* studies are performed, any specification limits for relevant parameters, e.g., APSD, physical characteristics for the active substance (see section 4.2.2.1), and particle size for the excipients, must be based on the batches used for substantiation of *in vitro* equivalence.

Development of a pMDI should always include testing with at least one specific spacer or holding chamber appropriate for the intended patient population (e.g., paediatrics, adults when there may be a

need to facilitate administration of the relevant dose). If a spacer is recommended in the SmPC of the reference medicinal product, this spacer should be used for comparison. Studies required to demonstrate therapeutic equivalence are described in Guideline on the requirements for demonstrating therapeutic equivalence between orally inhaled products (OIP) for asthma and chronic obstructive pulmonary disease (COPD) (CPMP/EWP/4151/00 Rev. 2).

4.4. Product information

Besides the general requirements, some specific information for inhalation medicinal products needs to be included in the Summary of Product Characteristics (SmPC) and the Package Leaflet (PL).

- *Strength of the medicinal product:* The strength should be expressed as the amount per delivered dose (ex-actuator), preferably in terms of the active moiety. The principle to use metered dose (ex-valve) may be applicable in some specific cases. For example, if the approved reference medicinal product has a strength expressed as metered dose, it is strongly recommended that the product, subject of an abridged application, applies the same principles as the reference medicinal product.
- *Qualitative and quantitative composition:* For clarity, both the amount per delivered dose and metered dose should be declared. The principle used for expression of strength should be stated first.
- *Administration and handling:* Relevant instructions for the correct administration and handling should be clearly described including directions with respect to the following items (if applicable):
 - shaking requirements
 - 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 spacer/holding chamber
 - the cleaning requirements of the delivery device and its components
 - 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, delivery rate of the active substance and total active substance delivered.
 - Information regarding dose counter/dose indicator or instructions on how to determine that (almost) all doses have been used.
- *Excipients:* If lactose is an excipient from bovine origin the relevant warning for cow's milk protein should be included. Other relevant warnings in accordance with the NtA 2C Guideline on excipients and its Annex should also be included.

For inhalation powders in hard capsules the capsule shell is considered as an excipient and the components should be stated under a separate subheading "Capsule shell".
- *Special precautions for storage:* for pMDI 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." Temporary storage deviations, such as temperatures below or above the recommended range, should be described.
- *Nature and contents of container:* The type of delivery device and its components should be listed. A visual description of the inhaler delivery device should be included.

4.5. Lifecycle management

Inhalation products, in particular DPI and pMDI, are considered as specialised pharmaceutical forms, in respect to the current guideline on process validation (EMA/CHMP/CVMP/QWP/BWP/70278/2012 Rev. 1). Exemption from a non-standard manufacturing process may be accepted if adequately justified by the manufacturer, on a case-by-case basis, as described in the above-mentioned guideline.

For any proposed change, a risk assessment should be performed to determine its impact on quality, safety or efficacy of the product. The following changes may be considered to have a significant impact:

- Change in the physicochemical state and/or thermodynamic activity of the active substance.
- Change in the qualitative and/or quantitative composition of excipients.
- Change in the geometry or material of the delivery device or delivery device components.
- Change of suppliers in delivery device and/or spacer devices for pMDI or nebulisers.
- Change in the manufacturing process, e.g.:
 - Change in a single Critical Process Parameter.
 - Changes in a number of non-Critical Process Parameters.
- Change in batch size of the finished product.
- Any other change that affects the *in vitro* APSD.

It should be noted that the list is not exhaustive, and, depending on the finished medicinal product characteristics, other changes might also have a significant impact. In all cases, the change should be supported by appropriate and representative batch data for all critical quality attributes before and after the proposed change. In addition, *in vivo* studies may also be required, unless otherwise justified.

5. Nasal medicinal products

Inhalation and nasal medicinal products have many similarities and therefore, most of the requirements specified for inhalation medicinal products in section 4 also apply for nasal medicinal products. One difference between inhalation and nasal medicinal products is the desired particle/droplet size of the finished medicinal product. For inhalation medicinal products the particles/droplets need to be in the respirable size, while for nasal medicinal products these small particles may reach the lung and give unwanted effects. Only requirements and characteristics unique for nasal medicinal products are specified in this section.

5.1. Active substance (S)

The requirements are similar as described for inhalation medicinal products, see section 4.1.

5.2. Finished medicinal product (P)

5.2.1. Description and composition of the finished medicinal product (P.1)

The complete qualitative and quantitative composition should be specified including excipients and any other components (e.g., solvents, gasses) removed during manufacturing. The amount of each active substance and excipient should be expressed in concentration (i.e., amount per unit volume or weight), as well as amount per container and per spray or drop, where applicable.

The primary packaging, type of delivery device and, if necessary, the secondary packaging or other components required for reasons of stability should be described. A detailed description of the packaging should be included in P.7.

5.2.2. Pharmaceutical development (P.2)

See section 4.2.2.

The tests indicated in Table 5.2.1 are normally conducted to characterise nasal medicinal products. Not all tests are necessary for all types of nasal medicinal products. If the tests described are not conducted due to the particular nature of the finished medicinal product or because assurance of the parameter has been established by other means, a justification for the omission should be provided. The pharmaceutical development studies should be performed as discussed below and in section 4.2.2. Tests for fine particle dose are not relevant for nasal medicinal products; however, the potential lung dose should be minimised and therefore, mass fraction below 10 µm should be evaluated.

Table 5.2.1. Pharmaceutical development studies for nasal medicinal products.

Pharmaceutical development study	Pressurised metered-dose nasal spray	Nasal powders, device-metered		Nasal liquids			
		Single-dose	Multi-dose	Single-dose drops	Multidose drops	Single-dose spray	Non-pressurised multidose metered-dose spray
(a) Physical characterisation	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(b) Minimum fill justification	Yes	No	Yes	Yes	Yes	Yes	Yes
(d) Extractables / leachables	Yes	No	No	Yes	Yes	Yes	Yes
(f) Particle / droplet size distribution	Yes	Yes	Yes	No	No	Yes	Yes
(g) Uniformity of delivered dose	Yes	Yes	Yes	No	No	Yes	Yes
(j) Actuator / nasal applicator deposition	Yes	Yes	Yes	No	No	Yes	Yes
(l) Shaking requirements	Yes ^a	No	No	Yes ^a	Yes ^a	Yes ^a	Yes ^a
(m, n) Initial & re-priming requirements	Yes	No	No	No	No	No	Yes
(o) Cleaning requirements	Yes	No	Yes	No	Yes	No	Yes
(p) Low temperature performance	Yes	No	No	No	No	No	No
(q) Performance after temperature cycling	Yes	No	No	No	No	Yes	Yes
(r) Effect of environmental moisture	Yes	Yes	Yes	No	No	No	No
(s) Robustness	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(t) Delivery device development	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(u) Preservative effectiveness / efficacy	No	No	No	No ^b	Yes ^c	No ^b	Yes ^c
(x) Spray pattern / plume geometry	Yes	Yes	Yes	No	No	Yes	Yes

^a For suspensions.

^b Single use formulations should preferably be preservative free, but if a preservative is present, it should be adequately justified.

^c If a preservative is present.

5.2.2.1. (a) Physical characterisation (P.2.1.1 and P.2.1.2)

The requirements are generally similar as described for inhalation medicinal products, see section 4.2.2.1. For nasal medicinal products rheological characterisation (e.g., thixotropy, viscosity), surface tension and density may also be relevant. For active substance(s) present in solid form, solubility, particle size, particle shape, density, rugosity, charge, polymorphic form and crystallinity may also be relevant.

5.2.2.2. (f) Particle / droplet size distribution (P.2.4)

The particle and/or droplet size distribution is considered as one of the CQAs of nasal medicinal products. It is therefore important to fully characterise the distribution during the development and ensuring consistency with the commercial product.

Testing should be conducted using a suitable method (e.g., multistage cascade impactor configured for nasal use and/or laser diffraction) to cover the whole particle/droplet size range. It should be demonstrated that deposition of the medicinal product is localised in the nasal cavity, i.e., by demonstrating that the vast majority of the particles/droplets are larger than 10 µm as measured by an appropriately qualified technique such as cascade impaction configured for nasal use (e.g., with an abbreviated impactor) or laser diffraction for solutions.

5.2.2.3. (g) Uniformity of delivered dose (P.2.4)

For multidose formulations, a study should be conducted to demonstrate the consistency of the delivered dose through the life of the container from the first dose (post-priming for products with priming instructions) until the last labelled dose. The study should be performed using the minimum recommended dose as stated in the product information (i.e., one or more actuations). The finished product should be used and tested according to the instructions given in the package leaflet with respect to storage orientation and cleaning requirements, as well as the minimum dosing interval. At least ten doses from the combination of the beginning, middle and end of a single container should be tested. The doses should meet the finished medicinal product specification limits for uniformity of delivered dose. Non-conforming results should be explained.

The doses between the last labelled dose and the last container exhaustion dose should also be tested and information on the tail-off profile should be provided where applicable. This testing may be waived if the container contains a lockout mechanism that prevents dosing beyond the labelled number of doses.

For single-dose formulations administered with a device (i.e., nasal spray and nasal powder), the *inter-container* variability should be studied to demonstrate consistency of the delivered dose. The study should be performed using a single actuation from at least ten containers. The doses should meet the finished medicinal product specification limits for uniformity of dosage units. Non-conforming results should be explained.

5.2.2.4. (u) Preservative effectiveness / efficacy (P.2.5)

For products containing a preservative a study should be conducted to demonstrate the effectiveness/efficacy of the preservative. Single-dose formulations for nasal use should be preservative free. In some cases, an excipient could have several different functions, e.g., a preservative and solubilising agent. If preservatives are used in the formulation their presence and amount should be adequately justified, and the minimum content limit should be demonstrated as microbiologically effective.

5.2.2.5. (x) Spray pattern / plume geometry (P.2.4)

Spray pattern and plume geometry should be studied to characterise the performance of the complete finished medicinal product, i.e., the formulation in combination with the delivery device. Both size and shape should be evaluated. The characteristics may be used to ensure consistency during development and as a baseline for comparison with a reference medicinal product or for future variations to an approved product.

5.2.3. Manufacture (P.3)

A detailed description of the manufacturing process for the finished medicinal product, including filling and packaging, should be included. If the particle size of the active substance(s), or of any excipient, is controlled, the particle size adjustment process (e.g., micronisation) should be described. Nasal medicinal products are in general considered to be manufactured by standard manufacturing processes. In some cases, the finished medicinal product may be considered complex (e.g., suspensions or low active substance content) as described in the guideline on process validation (EMA/CHMP/CVMP/QWP/BWP/70278/2012 Rev1). P.3.3 and P.3.4 should be sufficiently detailed and include both critical and non-critical process parameters justified by reference to the manufacturing process development undertaken.

The controls for critical steps and intermediates should be described. Appropriate in-process controls should be established based on CQAs and CPPs determined during the development studies, e.g., assay, homogeneity, osmolality, pH, viscosity, consistency of filling, quality of sealing.

The manufacturing process 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.

5.2.4. Control of excipients (P.4)

The requirements are similar as described for inhalation medicinal products, see section 4.2.4.

5.2.5. Control of the finished medicinal product (P.5)

This section describes specification tests specific to nasal medicinal products. Standard finished medicinal product specification tests (e.g., identification, degradation products, pH, viscosity) have not been included, but it is expected that these tests are included in the specifications. Other guidance documents (e.g., ICH Q6A) should be consulted in this regard.

Acceptance criteria should be set based on the observed ranges of variability in batches that showed acceptable performance *in vivo* (i.e., pivotal clinical batches and/or batches used in pivotal pharmacokinetic studies), if applicable, or *in vitro* comparative studies. Process capability may also be considered. In addition, different tests and limits may apply at release versus shelf-life; differences should be clearly described and justified.

Table 5.2.2 includes the tests normally included in the finished medicinal product specifications for nasal medicinal products. Not all tests are necessary for all types of nasal medicinal products, as noted in table 5.2.2. The tests are discussed below and in section 4.2.5.

Table 5.2.2. Finished product specification tests for nasal medicinal products.

Finished product specification test	Pressurised metered-dose nasal spray	Nasal powders, device-metered		Nasal liquids			
		Single-dose	Multi-dose	Single-dose drops	Multidose drops	Single-dose spray	Non-pressurised multidose metered-dose spray
(a) Description	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(b) Assay	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(c) Moisture content	Yes	Yes	Yes	No	No	No	No
(d) Mean delivered dose	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Table 5.2.2. Finished product specification tests for nasal medicinal products.

Finished product specification test	Pressurised metered-dose nasal spray	Nasal powders, device-metered		Nasal liquids			
		Single-dose	Multi-dose	Single-dose drops	Multidose drops	Single-dose spray	Non-pressurised multidose metered-dose spray
(e) Uniformity of delivered dose	Yes	Yes	Yes	No	Yes	No	Yes
(f) Content uniformity / uniformity of dosage units	No	No	No	Yes	No	Yes	No
(h) Leak rate	Yes	No	No	No	No	No	No
(i) Microbial / microbiological limits	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(j) Sterility	No	No	No	Yes ^a	Yes ^a	Yes ^a	Yes ^a
(l) Preservative content	No	No	No	No	Yes ^b	No	Yes ^b
(m) Number of deliveries per container	Yes	No	Yes	No	No	No	Yes
(n) Particle / droplet size distribution	Yes	Yes	Yes	No	No	Yes	Yes

^a If the product is sterile.

^b If a preservative is present.

5.2.5.1. (n) Particle / droplet size distribution

Limits should be included for an allowed range for the median diameter and on the sub 10 µm particles/droplets. The sub 10 µm particles / droplets should be tested using a validated method (e.g., cascade impaction or an abbreviated impactor configured for nasal use or for nasal spray laser diffraction may be used if adequately cross validated to cascade impactor. For solutions, laser diffraction may be used). The median diameter can be tested with a validated laser diffraction method. The limits should be qualified by the results of batches used for *in vivo* studies (i.e., pivotal clinical batches and/or batches used in pivotal pharmacokinetic studies), or *in vitro* comparative studies.

5.2.6. Container closure system (P.7 and R)

The requirements are similar as described for inhalation medicinal products, see section 4.2.6.

5.2.7. Stability (P.8)

The requirements are similar as described for inhalation medicinal products, see section 4.2.7.

5.3. Therapeutic equivalence

The quality requirements to be considered for the development of a medicinal product which is intended to be authorised by an abridged application are not different from the development of the nasal medicinal product used as reference medicinal product. Quality data requirements as described in this guideline should be met, supplemented by appropriate comparative quality and clinical data with respect to the chosen reference medicinal product.

For nasal medicinal products claiming essential similarity to a reference medicinal product, studies required to demonstrate therapeutic equivalence may depend on the intended site of action of the active substance(s), local or systemic effect. Note for Guidance on the clinical requirements for locally applied, locally acting products containing known constituents (CPMP/EWP/239/95) and Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) may be consulted.

In order to conclude *in vitro* therapeutic equivalence, the following parameters should be considered in the comparison between test and reference product, when relevant:

- Qualitative and quantitative composition
- Actuation volume, active substance content in single actuation, or mass of single dose
- Droplet size distribution
- Mass of droplets smaller than 10 µm
- Physical characteristics of the active substance (see section 5.2.2.1)
- Spray pattern / plume geometry
- Rheological properties (e.g., thixotropy, viscosity)
- Surface tension
- pH
- Density
- Osmolality
- Buffer capacity

Other parameters may be applicable depending on the finished medicinal product characteristics. The chosen and omitted parameters should be discussed and justified. The *in vitro* equivalence should be performed and evaluated based on a predefined study protocol including methods of comparison and acceptance criteria. Any differences should be accompanied by a rationale as to why the differences will not result in different deposition and/or absorption characteristics.

5.4. Product information

Besides the general requirements, some specific information for nasal medicinal product needs to be included in the Summary of Product Characteristics (SmPC) and the Package Leaflet (PL).

- *Strength of the medicinal product:* For the expression of strength in the medicinal product name of a centrally authorized product, QRD recommendations are normally applied. However, a decision on the most appropriate strength in the name of a medicinal product may be taken on a case-by-case basis to convey the most relevant information to the healthcare professionals and ensure safe and effective use of the medicinal product, e.g. mg per spray (see Table 5.4.1), preferably in terms of the active moiety. It is strongly recommended that the product, subject of an abridged application, applies the same principles as the reference medicinal product.

Table 5.4.1. Nasal preparations – expression of strength in product name.^a

Pharmaceutical form	Container	Preferred expression	Format
Pressurised metered-dose nasal spray	Single-dose	Amount per dose	z mg
	Multidose	Amount per spray	x mg/spray
Non-pressurised multidose nasal spray	Single-dose	Amount per dose	z mg
	Multidose	Amount per spray	x mg/spray
Nasal powders	Single-dose	Amount per dose	z mg
	Multidose	Amount per actuation	x mg/actuation
Nasal drops	Single-dose	Amount per dose	z mg
	Multidose	Amount per drop	x mg/drop

^a It is strongly recommended that the product, subject of an abridged application, applies the same principle as the reference medicinal product.

- *Qualitative and quantitative composition:* Both the amount of active substance per actuation/drop and per millilitre should be stated.
- *Administration and handling:* Relevant instructions for the correct administration and handling should be clearly described, including directions with respect to the following items (if applicable):
 - shaking requirements
 - the need for priming and re-priming

- orientation of the nasal drug delivery device and position of the patient during actuation
- the cleaning requirements of the delivery device and its components
- *Excipients*: Relevant warnings in accordance with the NtA 2C Guideline on excipients and its Annex should be included.
- *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.*” Temporary storage deviations, such as temperatures below or above the recommended range, should be described.
- *Nature and contents of container*: The type of the delivery device and its component materials should be listed. A visual description of the delivery device should be included.

5.5. Lifecycle management

For any proposed change, a risk assessment should be performed to determine its impact on quality, safety or efficacy of the medicinal product. The following changes may be considered to have a potential significant impact:

- Change in the physicochemical state and/or thermodynamic activity of the active substance(s).
- Change in the qualitative and/or quantitative composition of excipients.
- Change in the geometry or material of the delivery device or device components.
- Change of suppliers in delivery device.
- Change in the manufacturing process, e.g.:
 - Change in a single Critical Process Parameter.
 - Changes in a number of non-Critical Process Parameters.
- Any other change that affects the particle/droplet size distribution, spray pattern or plume geometry.

Please note that the list is not exhaustive, depending on the medicinal product characteristics other changes might also have a significant impact. In all cases, the change should be supported by appropriate and representative batch data for all critical quality attributes before and after the proposed change. In addition, *in vivo* studies may also be required, unless otherwise justified.

Definitions

Activation:	The act of setting in motion the delivery device.
Actuation:	The release of active substance from the 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 active 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 active substance to the respiratory tract (inhalation medicinal product) or the nasal and/or pharyngeal region (nasal medicinal product).
Dose:	Quantity of the active substance to be administered at one time, as specified in the product information; also, the number of actuations providing that quantity of active substance. One dose may consist of several actuations.
Dosing interval:	The recommended length of time between doses, as specified in the product information.
Dry powder inhaler (DPI), device-metered:	An inhalation medicinal product containing a reservoir of powder which is measured into individual actuations by the delivery device.
Dry powder inhaler (DPI), pre-metered:	An inhalation medicinal product containing pre-measured actuations, usually in capsules or blister packaging.
Ex-actuator:	Not including the quantity of active substance deposited on the actuator.
Extractables:	Compounds which may be extracted from the container closure system by using stressful conditions.
Fine particle dose (FPD):	The quantity of active substance in an inhalation medicinal 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. Fine particle mass (FPM) may be used interchangeably.
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: $(D_{84.13\%} / D_{15.87\%})^{1/2}$.
Holding chamber:	An add-on device (spacer) for use with a pressurised metered-dose inhaler (pMDI) consisting of a reservoir with an inhalation valve to retain the aerosol until inhalation by the patient. It may also have an exhalation valve to prevent the patient from breathing into the reservoir.
Inhalation medicinal product:	A finished medicinal 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 active substance (usually on a per actuation basis) declared on the label of the medicinal 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 active 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 product information, expressed as delivered dose.
Nasal medicinal product:	A finished medicinal 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 drug 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 drug delivery device containing an aqueous solution, suspension or emulsion, which delivers one dose in one (or more) actuation(s).
Plume geometry:	Spray characteristics describing a side view of the aerosol cloud parallel to the axis of the plume, reported as the spray angle and plume width.
Pressurised metered-dose inhaler (pMDI):	An inhalation medicinal product containing one or more propellants in a pressurised delivery device.
Pressurised metered-dose nasal spray:	Medicinal product for nasal administration containing one or more propellants in a pressurised delivery device.
Preparations for nebulisation:	A liquid inhalation medicinal product administered via a commercially marketed nebuliser.
Spacer:	An add-on device for use with a pressurised metered-dose inhaler (pMDI) consisting of a reservoir into which the aerosol is dispensed.
Spray:	See actuation.
Spray pattern:	Spray characteristics describing the size and shape of the emitted plume.
Target delivered dose:	The quantity of active substance expected to be released from the delivery device in the number of actuations equivalent to a dose.
Target delivery amount:	The quantity of active substance expected to be released from the delivery device (i.e., ex-actuator or ex-device) in one actuation.