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Guideline on the pharmaceutical quality of inhalation and nasal medicinal products

Draft

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This guideline replaces the guideline on pharmaceutical quality of inhalation and nasal products (EMEA/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.

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

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 (EMEA/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.

General comment:

- EFA highly welcomes EMA efforts to ensure inhalation and nasal products meet high-quality standards, safeguarding their safety and efficacy. With the considerable advancements our community of member associations active in allergy and airways diseases is witnessing within this field, quality guidelines must evolve to fully encompass innovation in medicinal products. EFA also applauds the research commitment to advance treatments and disease management for allergy, asthma and chronic obstructive pulmonary disease (COPD) patients. Currently, around 30 inhalation products are authorized for COPD, 8 inhalation products for asthma and 4 hybrid products for both diseases. Regarding nasal products, 2 have been approved in the EU including nasal sprays for allergic rhinitis as well as for anaphylaxis. The latter entails a new and innovative way of treating this severe allergic reaction. EFA also proposes including the list of disease areas these products are mostly used for in the guideline, including allergy, asthma and COPD.

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. 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.

EFA comment (line 75):

- EFA encourages the EMA to include "abridged application" in the list of definitions.

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.

EFA comment (lines 84-88):

- We note that all the types of medicinal products that fall within the scope of the guideline are products used with a medical device called drug-device combination products. EFA proposes to clarify this and recognize the products as combination products to improve their regulatory process. The development and evaluation of combination product remains fragmented within the EU with the medicinal product and device being authorized through different procedures but then centrally approved as one product, which results in limited consultations with patients on the development and performance of platform medical devices. EFA therefore encourages the EU to review current pharmaceuticals legislation to better capture, evaluate, authorize and monitor combination products because they are exponentially growing, including digital aids, and could be recognized as a distinct product category through a separate legislation that puts patients' safety and usability at the center.

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. 1),
- 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 replacing hydrofluorocarbons as propellants in oral pressurised metered dose inhalers (EMA/CHMP/83033/2023),
- European Pharmacopeia.

4. Inhalation medicinal products

4.1. Active substance (CTD 3.2.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 micronisation process and the in-process controls should be provided. Sufficient details need to be included in Module 3.2.S and referenced in Module 3.2.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*.

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.

EFA comment (line 121):

- EFA recommends clarifying the need for control of microbiological quality and in what circumstances such control does not need to be performed. The high-quality of inhalation and nasal products must be ensured, including control of microbiological quality when needed.

If alternative sources of the active substance are proposed, evidence of equivalence should include appropriate physical characterisation and *in vitro* performance studies (see section 4.2.2 Pharmaceutical Development).

4.2. Finished medicinal product (CTD 3.2.P)

4.2.1. Description and composition of the finished medicinal product (CTD 3.2.P.1)

The complete qualitative and quantitative composition should be specified including any excipient (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), total amount per container and amount per actuation should be defined both as metered and delivered dose.
The primary packaging, type of inhaler 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 Module 3.2.P.7.

4.2.2. Pharmaceutical development (CTD 3.2.P.2)

Pharmaceutical development studies are conducted to demonstrate that the type of formulation along with the pharmaceutical form, manufacturing process, container closure system, 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 usability studies to cover how the finished medicinal product should be used.

EFA comment (lines 140-141):

- Depending on the patients' characteristics and needs, the dose and usage of inhalation products

differs, calling for multiple usability studies to encompass allergy, asthma and COPD patients' realities. Therefore, EFA proposes this is reflected in the guideline, to ensure usability is tested for all patients included in the patient population.

Quality by Design (QbD) may be used as a development tool. The development studies should be conducted on more than one batch, to account for both inter/intra batch variability, and it is recommended to include a minimum of three batches with at least ten inhalers from each batch. The development batches should be representative of the commercial medicinal product; however, pilot scale batches may be acceptable. In the case of multiple strengths and multiple package sizes (i.e., number of doses in each inhaler), a justified bracketing and/or matrixing design among the different strengths and/or pack sizes may be used.

EFA comment (line 144):

- EFA proposes to change the wording from "inhalers" to "inhalation products" to encompass all inhalation products (inhalers and nebulisers).

Sufficient data should be provided to support the proposed specification 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. All batches used in pivotal clinical 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

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	
(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	No	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	No	Yes
(p) Low temperature performance	Yes	No	No	No	No	No

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	
(q) Performance after temperature cycling	Yes	No	No	No	No	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[b]	Yes[b]	Yes[b]
(v) Compatibility	No	No	No	Yes	Yes	No
(x) Spray pattern / plume geometry	Yes	No	No	No	No	Yes

[a]For suspensions.
[b]If a preservative is present.

4.2.2.1. (a) Physical characterisation (CTD 3.2.P.2.1.1 and 3.2.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 micronisation process itself 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 (CTD 3.2.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 on 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.

EFA comment (lines 181-183):

- EFA would like to stress that even though it could really serve patients to manage their care, their dosage and their medicines reserves, certain containers do not present an ml scale for patients to assess how much product is left. We recommend EMA to require manufacturers and producers to include a ml scale in non-opaque glass containers of liquid medicines.

4.2.2.3. (c) Extractable volume (CTD 3.2.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 (CTD 3.2.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. The principles described in relevant guidelines (e.g., CPMP/QWP/4359/03 Guideline on plastic immediate packaging materials) should be taken into account. 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 medicinal product or to the point equilibrium is reached, if sooner.

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. Safety risk assessment principles for limiting potential carcinogenic risk as outlined in ICH M7 should be used. If applicable a tabulated list of potential genotoxic substances and their acceptability in respect to safety concerns should be provided. If there are no safety concerns with the type and level of leachables detected, routine monitoring of leachables would not be necessary. 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 (CTD 3.2.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 sample size greater than the minimum number of actuations, 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 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. Justification for not conducting this test (e.g., for low dosed medicinal products) should be provided. The fine particle dose of the minimum number of actuations in the recommended dose should be determined according to the finished medicinal product specification fine particle dose method, modified only as necessary to accommodate the reduced sample size. If this study is not feasible due to the sensitivity of the analytical method, data supporting this claim should be provided.

EFA comment (lines 213-225):

- EFA proposes to clarify earlier in the guideline the difference between inhalation products and nasal products regarding particle size, which is now explained only under chapter 5 (lines 698-700). Inhalation products should have a particle size < 5 µm so to reach the lungs, while nasal products are often intended for local action and small particles are unwanted. This would also clarify the need to determine the fine particle dose for inhalation products.
- EFA also urges EMA to take into consideration the possible implication of the testing exception for low dosed medicinal products (line 221), as low doses are often used in the paediatric population.

4.2.2.6. (f) Aerodynamic particle / droplet size distribution (CTD 3.2.P.2.4)

The aerodynamic particle size distribution (APSD) is considered as 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 used for *in vivo* studies (pivotal clinical and/or comparative), 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, 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 APSD or group of stages should be determined and evaluated for clinical impact.

For solutions for nebulisation 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 (CTD 3.2.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 containers

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.

EFA comment (lines 251-253):

- EFA would like to stress that the testing procedure as described often does not reflect the real-world usage. Examples of real-world situations not tested by such procedures are patients traveling with their inhalation product (e.g. if lifesaving for the patient) or family members using different inhalation products but the same chamber/spacer. EFA suggests including real-life testing beyond laboratory testing to ensure uniformity of delivered dose and FPD at all times.

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.

EFA comment (lines 259-262):

- EFA would like to stress that it is currently often not possible for patients to identify when the last dose of a pressurized metered dose inhalation product (pMDI) is administered if the device does not include a lockout mechanism. This might lead to continued use of an "empty" product, potentially leading to severe health implications.

4.2.2.8. (h) Uniformity of delivered dose and fine particle dose over patient flow rate range (CTD 3.2.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 effort of the intended patient population. Using three fixed flow rates in a range of about 30-90 L/min is typically acceptable.

EFA comment (lines 265-268):

- EFA praises EMA for taking into consideration the potential differences in inspiratory effort of the intended patient population. EFA further stresses that the study testing consistency of delivered dose and fine particle dose as described here should be inclusive regarding disease, disease severity and age differences to ensure product consistency when actuated by any type of patient or caregiver.

4.2.2.9. (i) Aerodynamic particle size distribution and delivered dose with spacer/holding chamber use (CTD 3.2.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 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 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 2 second 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 are required for minimising the impact of electrostatic interference.

EFA comment (lines 271-284):

- EFA praises EMA for attempting to better reflect reality by altering the testing of aerodynamic particle size distribution (APSD) and delivered dose with a chamber/spacer to mimic real patient performance. Chambers/spacers are often used by children and administration is then often done by caregivers. Additionally, as mentioned in the comment on line 251-253, family members using different inhalation products often "share" a chamber/spacer without precautions. Therefore, EFA suggests to further stress in the guideline the importance of testing the APSD and delivered dose with a chamber/spacer in such real-world situations to ensure test results reflect allergy, asthma and COPD patients' use and choices.

4.2.2.10. (j) Actuator / mouthpiece deposition (CTD 3.2.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 (CTD 3.2.P.2.4)

To allow an assessment of the complete delivery profile of the medicinal product used for *in vivo* studies (pivotal clinical and/or comparative) or *in vitro* characterisation and/or 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 (CTD 3.2.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.

EFA comment (lines 297-298):

- EFA proposes to also test if the shaking instructions are clear for patients and caregivers. The need/reason for shaking the product should be explained as well, to further enhance patients' adherence.

4.2.2.13. (m) Initial priming of the container (CTD 3.2.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.

EFA comment (lines 305-306):

- EFA stresses that adequate and complete instructions on storage orientation as well as implications and actions to take in case of incorrected storage should be added to the product information if storage orientation has a significant effect on the medicinal product and delivered dose, as this could constitute a safety and efficacy risk for allergy, asthma and COPD patients.

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.

EFA comment (line 309):

- EFA proposes to also test if priming instructions are adequate and clear for patients and caregivers. EFA also suggests adding explanations on the importance and rationale of each step in the priming process to improve the patients and caregivers' technique and adherence, and empower them with knowledge about how their highly technical medicine functions.

4.2.2.14. (n) Re-priming of the container following storage (CTD 3.2.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 always is 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 or the highest number of re-priming actuations).

EFA comment (line 320-321):

- EFA supports the obligation for user-acceptance testing of the re-priming instructions. As commented for 4.2.2.12 and 4.2.2.13, EFA proposes to also require user-acceptance testing for shaking instructions and priming instructions (comments lines 305-306 and 309).

4.2.2.15. (o) Cleaning requirements (CTD 3.2.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 device is designed to have the mouthpiece removed for periodic cleaning, testing should be

performed in accordance with the instructions given in the labelling, and as a worst case without removal and cleaning.

This study could be combined with 4.2.2.7 (Uniformity of delivered dose and fine particle dose through container life).

EFA comment (line 326-334):

- EFA encourages EMA to perform user-acceptance testing for the cleaning instructions of all combination products, as cleaning instructions are rarely well-described and explained to patients and caregivers and guidance by health care professionals or pharmacists often lacks. Cleaning instructions should be added to the product information leaflet of all combination products, especially for those products requiring regular cleaning (for example, after each dose).

4.2.2.16. (p) 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 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.

Instructions regarding cold temperature use should be provided in the product information. If this study is not conducted, information on how and how long to warm the container should be provided. Alternative approaches for inhalation medicinal products which do not tolerate low temperatures should be fully justified.

4.2.2.17. (q) Performance after temperature cycling (CTD 3.2.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, related substances and moisture content should be performed. Any changes from initial results should be assessed for their significance.

4.2.2.18. (r) Effect of environmental moisture (CTD 3.2.P.2.4)

The effect of environmental moisture on product performance of unprotected finished medicinal product 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 are expected, as a minimum. For pre-metered products using capsules, special attention should be paid 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.

EFA comment (line 335-365):

- EFA encourages EMA to perform user-acceptance testing for the instructions regarding cold temperature use of a product as well as the warming instructions if needed.
- EFA proposes to clarify the meaning of an "unprotected finished medicinal product" (line 359-360)
- Additionally, EFA also encourages EMA to request patient and caregiver information of the implications of temperature and moisture on the safety, efficacy and use of the inhalation product. Patients should be able to prevent these impacts as well as be able to recognize if the product is impacted (e.g. if it was exposed to too much moisture) and take appropriate action.

366 ***4.2.2.19. (s) Robustness (CTD 3.2.P.2.4)***

367 The product performance should be investigated under conditions to simulate patient use. This includes
368 activating the delivery device at the frequency indicated in the product information. Carrying the
369 delivery device between use, simulation of dropping the delivery device and the robustness of any
370 lockout mechanism, digital sensor etc., should be considered.

EFA comment (line 367-370):

- EFA proposes to add testing of robustness throughout the lifecycle of the inhalation product, as the product may be used for long periods of time (i.e. six months) if it is multi-dose.

371 Vibrational stability of powder mixtures should be demonstrated in order to simulate vibrations during
372 transport and use. Significant variations in the delivered dose and/or fine particle dose should be fully
373 discussed in terms of the safety and efficacy of the medicinal product.

EFA comment (line 371-372):

- EFA praises EMA for taking into consideration transportation of the inhalation product. As mentioned before, patients often move around and travel with their inhalation products, especially those who need it for lifesaving reasons. EFA also stresses that for those reasons, certain inhalation products cannot be too sensitive to mobility circumstances such as vibrations, hits or temperature, leading to quality aspects that should be taken into account.

374 Dropping of the device should be investigated. The dropping simulation should be performed towards
375 the end of the life of the product (e.g., at dose 180 for a 200 doses product) in order to assess the
376 effect of finished medicinal product accumulated on the mouthpiece, or any other part of the device,
377 during the life-time of the device. Significant variations in the delivered dose and/or fine particle dose
378 should be discussed in terms of the safety and efficacy of the medicinal product. Appropriate handling
379 instructions should be established based on the results obtained and included in the product
380 information.

EFA comment (line 378-380):

- EFA encourages EMA to require user-acceptance testing for the handling instructions after dropping of the product to ensure safe and effective use of the inhalation product, as well was guidelines on how to proceed in the event there is suspicion the quality of the product cannot be maintained.

381 4.2.2.20. (t) Delivery device development (CTD 3.2.P.2.4 and 3.2.R)

382 The development of the delivery device should be described. Any changes implemented in the design
383 (e.g., change of component materials) and/or manufacturing process of the delivery device (e.g., scale
384 up from single cavity to multiple cavity tooling) during the development of the medicinal product
385 should be discussed in terms of the impact on the product performance characteristics (e.g., delivered
386 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.

EFA comment (line 382-388):

- EFA encourages EMA to promote early patients' participation in the development stage of delivery devices, to ensure optimal use of the inhalation product as well as patient adherence. A variety of medical devices exist (e.g. pressurised and non-pressurised metered-dose inhalers (MDI), dry powder inhalers (DPI), nebulisers), so the patient input should be considered in the decision-making process deciding on a certain device as well as in the development stage.

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.

For multidose inhalation medicinal products each unit should have a dose counter to give the patient indication of when the number of actuations stated on the label has been delivered.

4.2.2.21. (u) Preservative effectiveness / efficacy (CTD 3.2.P.2.5)

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

4.2.2.22. (v) Compatibility (CTD 3.2.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 (CTD 3.2.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 pump.

4.2.3. Manufacture (CTD 3.2.P.3)

A detailed description of the manufacturing process for the finished medicinal product, including filling and packaging, should be included. If the active substance or any excipient is micronised after being received from the supplier, the micronisation process 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, in particular DPI and pMDI, are considered specialised dosage forms manufactured by non-standard manufacturing processes. Module 3.2.P.3.3 and 3.2.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 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 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 inhalers, blister sealing for DPI). The yield of the 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 (CTD 3.2.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 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 (pivotal clinical and/or comparative), although *in vitro* data (from multistage impaction/impinger) may suffice to demonstrate the suitability of the extremes of the limits.

EFA comment (line 443):

- Regarding the presence of lactose as excipient, this could have severe health implications as lactose can cause allergic reactions. Not only immediate or recognizable reactions should be considered, but also potential long-term or cumulative adverse health effects of lactose-containing medicines. This is especially important for asthma patients with food allergy co-mordibity, as there is an increased risk of more severe allergic reactions with respiratory symptoms due to hypersensitive airways. EFA therefore highly encourages developers to prefer the use of excipients that do not cause irritation and inflammation. If lactose is used, allergen/intolerance and adverse reactions information should be clearly disclosed in the package leaflet.

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

EFA comment (lines 448-449):

- As mentioned for the active substances (4.1, line 121), EFA encourages to further clarify controls of microbiological quality and in what circumstances the control does not have to be performed. The high-quality of inhalation and nasal products must be ensured, including control of microbiological quality when needed.

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 route of administration.

EFA comment (lines 458-460):

- EFA suggests EMA to further require studying of the potential impact on patient safety of known gas excipients used in MDIs that have been assessed to have a potential impact on the environment, including fluorinated greenhouse gases (F-gases). The new F-gases Regulation 2024/573 and its accompanying Implementing Regulation 2024/2174 will introduce new labelling rules for MDIs to be applied from 1 January 2025. While the transition and green labelling focuses on the environmental footprint of products containing F-gases, it is of utmost importance for EFA that respiratory patients who use MDIs containing F-gases are informed about the effects of inhaling F-gases on their health. Therefore, EFA suggests that the health implications of the use of these products are further clarified and are fully integrated in the package information leaflet.

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 (CTD 3.2.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 variation in batches that showed acceptable performance *in vivo.* 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.

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

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	
(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 ±5% should apply unless otherwise justified.

4.2.5.3. (c) Moisture content

The limit for moisture content should be established based on results seen in stability studies. If the results are stable throughout the shelf-life of the 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 ±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 device (intra-inhaler) and between devices (inter-inhaler). The tests should be conducted according to pharmacopoeial methods, or suitably validated alternatives. A single test combining intra/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/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.

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 per actuation 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 for clinical batches using the same method should be submitted.

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 e.g., 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 (pivotal clinical and/or comparative) and should be reported on a per actuation or per dose basis. Normally, it is considered that a specification range of up to ±25% is adequate for 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 the same analytical methods are used for the determination of fine particle dose concerning clinical batches as well as for the medicinal product intended for the market. Ranges wider than ±25% should be sufficiently justified by *in vivo* data. 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 be overlapping.

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 (CTD 3.2.P.7, 3.2.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.

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 should be described.

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.

All medical devices, including inhalers and nasal devices, have to fulfil the general requirements as outlined in the Medical Device Regulation (EU) 2017/745. The device shall meet the general safety and performance requirements set out in Annex I of Regulation (EU) 2017/745, which apply to it, taken into account its intended purpose. For medical 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. Module 3.2.R should include information related to demonstration of compliance of the 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 (CTD 3.2.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.

EFA comment (lines 601-602):

- As mentioned before, EFA stresses that adequate and complete instructions on storage orientation as well as implications and actions to take in case of incorrect storage should be added to the product information if storage orientation has a significant effect on the product performance, as this could constitute a safety and efficacy risk for allergy, asthma and COPD patients.

If the medicinal product includes secondary packaging in order to protect it from light and/or humidity (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) should be considered even though the product will be used for other indications than asthma or COPD.

If no *in vivo* studies are performed, any specification limits for relevant parameters, e.g., aerodynamic particle size distribution) for the finished product 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 the multidisciplinary guideline for OIP (CPMP/EWP/4151/00).

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).

- *Name of the medicinal product*: In accordance with the QRD recommendations on the expression of strength in the name of centrally authorised human medicinal products (EMA/707229/2009), the strength should be expressed as the amount per delivered dose (ex-actuator). 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 (i.e. an abridged application of that reference medicinal product) applies the same principle.
- *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 device and its components should be included.
    - 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.
- *Excipients:* If lactose is an excipient from bovine origin the relevant warning for cow's milk protein in accordance with the guideline on Excipients should be included.

EFA comment (lines 662-663):

- As mentioned in line 458-460, EFA suggests EMA to further require studies on the potential impact on patient safety of F-gases and to reflect the conclusions of those studies in the product information leaflets and labeling rules.

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 the device and its components should be listed. A visual description of the inhaler 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 device or device components.
- Change of suppliers in 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.
- Any other change that affects the *in vitro* APSD or *in vitro* dissolution release characteristics of the finished product.

It should be noted that the list is not exhaustive, and depending on the 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 (i.e., <5 μm) 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 (CTD 3.2.S)

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

5.2. Finished medicinal product (CTD 3.2.P)

5.2.1. Description and composition of the finished medicinal product (CTD 3.2.P.1)

The complete qualitative and quantitative composition should be specified including any excipient (e.g., solvents, gasses) removed during manufacturing. The amount 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 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 Module 3.2.P.7.

5.2.2. Pharmaceutical development (CTD 3.2.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. 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.

Table 5.2.1. Pharmaceutical development studies for nasal medicinal products.

			Nasal liquids			
Pharmaceutical development study	**Pressurised metered-dose nasal spray**	**Nasal powders, device-metered**	**Single-dose drops**	**Multidose drops**	**Single-dose spray**	**Non-pressurised multidose metered-dose spray**
(a) Physical characterisation	Yes[a]	Yes	Yes[a]	Yes[a]	Yes[a]	Yes[a]
(b) Minimum fill justification	Yes	Yes	Yes	Yes	Yes	Yes
(d) Extractables / leachables	Yes	No	Yes	Yes	Yes	Yes
(f) Particle / droplet size distribution	Yes	Yes	No	No	Yes	Yes
(g) Uniformity of delivered dose through container life	Yes	Yes	No	No	No	Yes

(j) Actuator / mouthpiece deposition	Yes	Yes	No	No	Yes	Yes

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 drops	Multidose drops	Single-dose spray	Non-pressurised multidose metered-dose spray
(l) Shaking requirements	Yes[a]	No	Yes[a]	Yes[a]	Yes[a]	Yes[a]
(m, n) Initial & re-priming requirements	Yes	No	No	No	Yes	Yes
(o) Cleaning requirements	Yes	Yes	No	Yes	No	Yes
(p) Low temperature performance	Yes	No	No	No	No	No
(q) Performance after temperature cycling	Yes	No	No	No	Yes	Yes
(r) Effect of environmental moisture	Yes	Yes	No	No	No	No
(s) Robustness	Yes	Yes	Yes	Yes	Yes	Yes
(t) Delivery device development	Yes	Yes	Yes	Yes	Yes	Yes
(u) Preservative effectiveness / efficacy	No	No	No[b]	Yes[c]	No[b]	Yes[c]
(x) Spray pattern / plume geometry	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

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.

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

The particle 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., laser diffraction or multistage cascade impactor with settings adjusted for nasal use). 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 cascade impaction (e.g., abbreviated impactor).

EFA comment (lines 734-735):

- EFA proposes to further clarify the term "vast majority" and specify a limit per molecule (or refer to where to find these limits) to ensure a safe use of the inhalation product.

5.2.2.3. (u) 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. 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 should be adequately justified, and the minimum content limit should be demonstrated as microbiologically effective.

5.2.2.4. (x) Spray pattern / plume geometry (CTD 3.2.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 pump. 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 (CTD 3.2.P.3)

A detailed description of the manufacturing process for the finished medicinal product, including filling and packaging, should be included. If the active substance(s) or any excipient is micronised after being received from the supplier, the micronisation process 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). Module 3.2.P.3.3 and 3.2.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 (CTD 3.2.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 (CTD 3.2.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 be 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 variation in batches that showed acceptable performance *in vivo*, 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.

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.

			Nasal liquids			
Finished product specification test	**Pressurised metered-dose nasal spray**	**Nasal powders, device-metered**	**Single-dose drops**	**Multidose drops**	**Single-dose spray**	**Non-pressurised multidose metered-dose spray**
(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) Uniformity of delivered dose	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[a]	Yes	Yes[a]	Yes
(j) Sterility	No	No	Yes[b]	Yes[b]	Yes[b]	Yes[b]
(l) Preservative content	No	No	No	Yes[a]	No	Yes[a]

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

(m) Number of deliveries per container	Yes	Yes	No	No	No	Yes
(n) Particle / droplet size distribution	Yes	Yes	No	No	Yes	Yes

[a] If a preservative is present.
[b] If the product is sterile.

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 with settings adjusted for nasal use or, for solutions, laser diffraction). 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 (pivotal clinical and/or comparative), or in case therapeutic equivalence has been substantiated by *in vitro* testing only, the test batches that have been used in the *in vitro* comparison.

5.2.6. Container closure system (CTD 3.2.P.7)

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

5.2.7. Stability (CTD 3.2.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, single actuation content, or mass of single dose
- Droplet size distribution
- Mass of droplets smaller than 10 µm

- Particle size distribution and morphological form of active substance for suspensions
- 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).

- *Name of the medicinal product:* In accordance with the QRD recommendations on the expression of strength in the name of centrally authorised human medicinal products (EMA/707229/2009), the strength should be expressed as the amount per unit volume (e.g. mg/mL), preferably in terms of the active moiety.
- *Qualitative and quantitative composition:* For nasal drops the amount per drop 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 device

EFA comment (lines 838):

- EFA proposes to clarify the instructions for patients and caregivers on the orientation of the nasal device for dose administration. The instructions should include the orientation needed during actuation and position of the patient when inhaling the product for optimal use and adherence.

    - the cleaning requirements of the device and its components

- *Excipients:* If lactose is an excipient from bovine origin the relevant warning for cow's milk protein in accordance with the guideline on Excipients 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 device and its component materials should be listed. A visual description of the 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 device or device components.
- Change of suppliers in 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.

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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:	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.
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: $(D84.13\% / D15.87\%)^{½}$
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 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).
Plume geometry:	Spray characteristics determined by 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 determined by size and shape.
Target delivered dose:	The quantity of active substance expected to be released from the 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.

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