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THE EURASIAN ECONOMIC COMMISSION

THE BOARD

RECOMMENDATION

September 7, 2018 **No. 17** Moscow

On the Guidelines on the Quality of Inhalation and Nasal Products

In accordance with Article 30 of the Treaty on the Eurasian Economic Union dated May 29, 2014 and paragraph 3 of Article 3 of the Agreement on Common Principles and Rules of Circulation of Medicinal Products within the Eurasian Economic Union dated December 23, 2014 and with a view to develop the Eurasian Economic Union Member States' common approaches to the requirements for the quality of inhalation and nasal products,

the Board of the Eurasian Economic Commission **recommends** the Eurasian Economic Union Member States to apply the Guidelines on the Quality of Inhalation and Nasal Products as laid down in the Annex in the course of research on the development of dosage forms, drafting of marketing authorization application dossier for inhalation and nasal medicinal products, examination of relevant documents as well as marketing authorization and modification of marketing authorization application dossier of these medicinal products after 6 months have elapsed from the date this Recommendation is published on the Eurasian Economic Union's official website.

Chairman of the Board of the Eurasian Economic Commission	T. Sargsyan

SEAL: *THE EURASIAN ECONOMIC COMMISSION * FOR DOCUMENTS*

ANNEX
to the Recommendation No. 17
of the Eurasian Economic Commission's
Board dated September 7, 2018

GUIDELINES
on the Quality of Inhalation and Nasal Products

I. General provisions

1. These Guidelines define general approaches to the quality and safety of inhalation and nasal products (hereinafter referred to as products) which should be included in the marketing authorization application dossier of medicinal products.

2. These Guidelines have been developed to be used by legal entities applying for marketing authorization of medicinal products in the territories of the Eurasian Economic Union Member States (hereinafter referred to as the Member States, the Union, respectively):

a) in the course of research on the development of dosage forms;

b) in the course of examination of relevant documents;

c) in the course of drafting of marketing authorization application dossier.

3. These Guidelines apply to human medicinal products intended for delivery of the active substance into the lungs, or to the nasal mucosa, with the purpose of evoking a local or systemic effect. The principles described in these Guidelines should also be considered for medicinal products used in clinical trials. It is not necessary that all testing would be conducted on all medicinal product batches used in clinical trial. However, extensive characterization of active pharmaceutical ingredients (active substances) and medicinal product batches used in clinical trials is necessary to qualify the product proposed for marketing in the territory of the Member States.

4. Quality aspects specific to medicinal products as well as the need for safety testing (e.g., for excipients and leachables) are covered by these Guidelines. Additional quality aspects (e.g., impurities, process validation, stability testing,

and specifications) as well as safety and efficiency aspects of medicinal products are not covered by these Guidelines.

These Guidelines do not contain recommendations on pharmaceutical development study designs (e.g., pumping test) and the analytical methods used primarily for medicinal products (e.g., multistage impactor analysis). The relevant information is contained in the Pharmacopoeia of the Union, Pharmacopoeias of the Member States, the main pharmacopoeias stipulated in Section VI of the Pharmacopoeial Harmonization Concept of the Eurasian Economic Union Member States approved by Decision No. 119 of the Eurasian Economic Commission's Board dated September 22, 2015 and international standards.

5. The criteria given in the Pharmacopoeia of the Union, and, if there is no such data, in the Pharmacopoeias of the Member States should be considered when implementing these Guidelines.

6. Since a variety of dosage forms and delivery devices is typical for medicinal products, it is allowed to make rationalized changes in the testing methodology.

7. The purpose of these Guidelines is to address matters related to the quality of medicinal products (including generic products) in the course of their marketing authorization. The instructions stipulated in these Guidelines should be taken into account when making decision on modification of marketing authorization application dossier of authorized medicinal products.

8. These Guidelines have been developed for medicinal products containing active pharmaceutical ingredients of synthetic and semi-synthetic origin. However, the general principles stipulated in these Guidelines should also be considered for other medicinal products.

9. These Guidelines cover the following medicinal products for the administration of the active substance to the lungs:

pressurised metered dose inhalers;

dry powder inhalers;

products for nebulization and non-pressurised metered dose inhalers;

pressurised metered dose nasal sprays;

non-pressurised metered dose nasal sprays;

sprays;

nasal powders and nasal liquids.

Liquid inhalation anaesthetics and nasal ointments, creams and gels are not covered by these Guidelines.

II. Definitions

10. For the purposes of these Guidelines, the concepts are used having the following meanings:

"activation" - means the act of preparation of the delivery device for release;

"pressurised" - means a dosage form which is a solution, emulsion or suspension of active substances under pressure of a propellant in a sealed package (pressurized pack) equipped with a delivery device which provides the actuation of the active substance in the form of dispersion of solid or liquid particles in the gas which size corresponds to the route of administration;

"pressurised metered dose inhaler" - means product for inhalation in a pressurised delivery device that delivers single dose in one (or more) actuation(s);

"pressurised metered dose nasal spray"-means product for nasal administration in a pressurised delivery device that delivers single dose in one (or more) actuation(s);

"leachables" - means compounds that may leach from the container closure system into the formulation under normal conditions of storage and use;

"actuation" - means the act of setting the delivery device in motion;

"geometric standard deviation (GSD)" - means a value obtained by analyzing the graph of dependence of cumulative fraction of mass less the stated cut-off diameter versus the cut-off diameter and calculated by the formula:

$$: GSD = \sqrt{\frac{D_{84,13\%}}{D_{15,87\%}}};$$

"dose" - means the quantity of the active substance to be administered at one time, as specified in the product information, which should be received in 1 administration regardless of the number of actuations;

"delivered dose" - means the quantity of active substance that is actually received by the patient (excluding the quantity of active substance deposited on the inhaler components);

"product for nebulization" - means a liquid inhalation product intended for use with a nebulizer;

"dosing interval" - means the recommended length of time between administrations of the medicinal product, as specified in the product information;

"mass median aerodynamic diameter (MMAD)" - means 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" - means the smallest recommended dose according to the product information, expressed as delivered dose;

"nasal product" - means a medicinal product (including the delivery device, where applicable) whose intended site of deposition is the nasal and (or) pharyngeal region, and the pharmacological action may be both local and systemic;

"non-pressurised metered dose inhaler" - means inhalation product in the form of an aqueous solution, suspension or emulsion, which delivers one dose in one (or more) actuation(s) with a portable delivery device;

"nebulizer" - means an inhaler that converts a liquid active substance to be sprayed into a dispersion in a gas medium using, as a rule, electrical energy. Nebulizer should provide the formation of dispersed particles of suitable size for the delivery of the medicinal product into the lungs;

"metered dose" - means the quantity of active substance contained in the delivery device’s metering chamber;

"dry powder inhaler, pre-metered" - means a medicinal product equipped with a dosing device and containing pre-measured amount of the active substance in powder form, usually in capsules or blister packaging;

"dry powder inhaler, device-metered" - means a medicinal product containing a reservoir of powder, which is measured into individual actuations using the delivery device;

"inhalation product" - means a medicinal product in solid or liquid dosage form intended for deposition of active substances in the form of vapors or dispersions of solid or liquid particles in a gas medium into the lungs to obtain a local or systemic effect;

"pumping" - means the process of filling of the delivery device that is a part of the container closure system with the medicinal product by means of consequent actuations;

"fine particle mass" - means the quantity of active substance presumably penetrating into the lungs during inhalation (particles with an approximate diameter of 1 to 5 μm);

"container closure system" - means the sum of packaging and closure components that together contain and protect the dosage form and may as well serve as a delivery device;

"spacer device" - means an accessory for inhalation, which is an intermediate reservoir for the product released for inhalation;

"spray" - means a more coarse-dispersed system compared to an aerosol that does not contain propellant; its contents is actuated due to air pressure generated by a mechanical pump-type nebulizer or during squeezing of a polymer package;

"non-pressurised metered dose nasal spray" - means nasal spray on form of an aqueous solution, suspension or emulsion, which delivers one dose in one (or more) actuation(s);

"therapeutic index" - means the ratio of the dose resulting in toxicity of the test system to the dose required to achieve the desired therapeutic effect in this test system;

"delivery device" - means the sum of components of the container closure system responsible for delivering the active substance to the respiratory tract (inhalation product) or the nasal and (or) pharyngeal region (nasal product);

"target delivered dose" -means the quantity of active substance expected to be released from the delivery device in one (or more) actuation(s) equivalent to a single dose;

"target delivery amount" - means the quantity of active substance expected to be released from the delivery device (ex-actuator or ex-device) in one actuation;

"extractables" - means compounds that may be extracted from the container closure system under stressful conditions.

III. Active substance specification

11. For medicinal products containing active pharmaceutical ingredient that is not a solution or liquid at any time during product manufacture, storage or use, the active substance specification should include a particle size test and indicate acceptance criteria. A validated particle sizing method (e.g., laser diffraction), with acceptance criteria set at multiple points across the size distribution, should be employed.

12. 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 defined. Acceptance criteria should be set based on the observed range of variation, and should take into account the particle size distribution of batches that showed acceptable performance in vivo, as well as for commercial batches of the medicinal product. Process capability and stability data should also be considered, provided the proposed acceptance criteria have been suitably qualified.

13. If an applicant uses active pharmaceutical ingredients sourced from various manufacturers, evidence of equivalence should include physical characterization and in vitro performance tests for each type of ingredients.

IV. Pharmaceutical development of the medicinal product

14. Pharmaceutical development studies of the medicinal product that subsequently ensure acceptable product performance of this product are conducted to:

a) determine the dosage form;

b) determine optimal parameters of the manufacturing process;

c) select optimal container closure system;

d) determine acceptable microbiological attributes;

e) obtain information on pharmacological properties of the medicinal product.

15. As a rule, the pharmaceutical development is conducted on several batches, and, therefore, that inter-batch variability of results is taken into account. For a single dose strength and a single container closure system, testing on 2 batches should be sufficient. For medicinal products packaged in container closure systems that also serve as the delivery device, tests should be conducted on several batches of the container closure system. In case of multiple dose strengths and several options of package sizes, a bracketing and (or) matrixing design may be used to reduce the necessary number of test samples. Rationale should be provided.

16. Sufficient data should be provided to rationalize the specifications proposed or to give adequate assurance that those performance characteristics that are not normally subjected to routine tests (e.g., pumping test) have been adequately studied. It is not necessary to test all batches used in clinical studies, but key batches used in pivotal clinical studies should be sufficiently characterized to rationalize the specifications for the medicinal product.

17. If the tests described are not conducted for certain reasons or assurance of the parameter has been established by another means, a rationale should be provided.

1. Inhalation products

18. The studies indicated in Table 1 are normally conducted to characterize products for inhalations (hereinafter referred to as inhalation products).

Table 1

Pharmaceutical development studies for inhalation products

Pharmaceutical development studies	Pressurised metered dose inhalers	Dry powder inhalers		Products for nebulization		Non-pressurised metered dose inhalers
		with a dosage device	pre-metered	single-dose	multidose	
Physical characterization	yes[1]	yes	yes	yes[1]	yes[1]	yes[1]
Minimum fill rationale	yes	yes	yes	yes	yes	yes
Extractables and leachables	yes	no	no	yes	yes	yes
Delivered dose uniformity and fine particle mass through container life	yes	yes	yes	no	no	yes
Delivered dose uniformity and fine particle mass over flow rate range	no	yes	yes	no	no	no
Fine particle mass with spacer use	yes	no	no	no	no	no
Single dose fine particle mass	yes	yes	yes	no	no	yes
Particle (droplet) size distribution	yes	yes	yes	yes	yes	yes
Actuator (mouthpiece) and other components deposition	yes	yes	yes	no	no	yes
Active substance delivery rate and total quantity delivered	no	no	no	yes	yes	no
Initial and re-pumping requirements	yes	no	no	no	no	yes

Pharmaceutical development studies	Pressurised metered dose inhalers	Dry powder inhalers		Products for nebulization		Non-pressurised metered dose inhalers
		with a dosage device	pre-metered	single-dose	multidose	
Cleaning requirements	yes	yes	yes	no	no	yes
Low temperature performance	yes	no	no	no	no	no
Performance due to temperature cycling	yes	no	no	no	no	yes
Effect of environmental moisture	yes	yes	yes	no	no	no
Robustness	yes	yes	yes	no	no	yes
Delivery device development	yes	yes	yes	yes	yes	yes
Preservative efficiency	no	no	no	yes[2]	yes[2]	yes[2]
Compatibility	no	no	no	yes	yes	no
Shaking requirements	yes[1]	no	no	yes[1]	yes[1]	yes[1]

[1] For suspensions.
[2] If a preservative is present.

19. As indicated in Table 1 of these Guidelines, different types of inhalation products require different tests. However, any study within the pharmaceutical development may be applicable to any inhalation product, depending on the information on inhalation product (e.g., shaking tests for certain dry powder inhalers). Depending on the operational characteristics of the delivery device, additional tests relevant to the performance of the inhalation product may be necessary.

20. Studies on the pharmaceutical development of generic products shall be conducted in accordance with the requirements of Appendix No. 1.

21. Information for consumers and health care professionals shall be specified in accordance with the requirements of Appendix No. 2.

22. Requirements for the modules of marketing authorization application dossier for inhalation products are given with the indication of the paragraphs of the common technical document (hereinafter referred to as the CTD) in accordance with the requirements stipulated in Annex No. 4 to the Rules of Marketing Authorization and Assessment of Medicinal Products for Human Use, approved by Decision No. 78 of the Eurasian Economic Commission's Council dated November 3, 2016.

Physical characterization (CTD 3.2.P.2.1.1 and 3.2.P.2.1.2)

23. Physical characteristics such as solubility, size, shape, density, rugosity, charge, and crystallinity of the active substance and (or) excipients may influence the homogeneity and reproducibility of the finished inhalation product with constant functionality. Tests for the development should include physical characterization of active pharmaceutical ingredient and excipients, relevant to their effect on the functionality of the inhalation product.

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

Minimum fill rationale (CTD 3.2.P.2.2.2)

25. For metered dose inhalers and device-metered dry powder inhalers, it should be demonstrated that the individual container minimum fill, as defined during the inhalation product manufacturing process, is sufficient for obtaining the number of activations of the dosing device (sprays, number of doses) included in the inhalation product information. The number of doses defined in the inhalation product information should meet the inhalation product specification, and requirements for such indicators as the delivered dose uniformity and fine particle mass should be met. Actuations required for pumping are not taken into account

when determining the total number of actuations of the dosing device (sprays, number of doses).

26. For pre-metered dry powder inhalers, the acceptance criteria for the fill weight of each metered unit should be rationalized in relation to such indicators as the delivered dose uniformity and fine particle mass.

27. For pre-metered dry powder inhalers, the acceptance criteria for the fill weight of each metered unit should be rationalized in relation to such indicators as the delivered dose uniformity and fine particle mass. For products for nebulization, the acceptance criteria the fill volume are determined in accordance with the principles set forth in these Guidelines.

Extractables and leachables (CTD 3.2.P.2.4)

28. For plastic and for rubber container closure system components not included in the Pharmacopoeia of the Union or Pharmacopoeias of the Member States that are in contact with the formulation during storage (e.g., valves), a test should be conducted to determine extractable and leachable profiles. Description and rationale of the test design (e.g., solvents used, temperature, shelf life (storage)) and the results should be provided. It should be determined whether any of the extractables are also leachables (released by the container) present in the formulation at the end of the shelf life of the inhalation product or upon reaching the equilibrium point, if it occurs sooner. Extractable and leachable profiles should also be determined for plastics and rubber container closure system components included in the Pharmacopoeia of the Union or Pharmacopoeias of the Member States.

29. For compounds that are potential leachables, identification should be conducted or experimental data on the impossibility of identification should be provided, safety assessments should be conducted in accordance with adequately established safety thresholds and reference to the data presented in Module 4 of marketing authorization application dossier (Annex No. 1 to the Rules of

Marketing Authorization and Assessment of Medicinal Products for Human Use) should be included.

30. Depending on the content levels and types of compounds detected, consideration should be given to include a test for leachables and permissible limits (acceptance criteria) for this test in the inhalation product specification and establish (if applicable) correlation between extractable and leachable profiles. If a correlation has been shown between the level of extractables and leachables in components and in raw materials, their control is carried out by including tests for extractables and leachables in components or in raw materials as well as permissible limits (acceptance criteria) for these tests in the specification. If safety is confirmed for the type and level of leachables detected, routine monitoring of leachables would not be necessary.

Fine particle mass through the container life and delivered dose uniformity (CTD 3.2.P.2.4)

31. A test should be conducted to demonstrate the consistency of the minimum delivered dose (e.g., one or more actuations) and the fine particle mass through the container life from the first dose (first post-pumping dose of inhalation products in accordance with inhalation product information) until the last dose, specified in the inhalation product information. The containers should be tested and used in accordance with the patient information leaflet (package leaflet) with respect to storage recommendations, cleaning requirements and minimum dosing interval. As a rule, a total of at least 10 doses should be tested at the beginning, middle and end of container use.

32. The doses obtained should meet the permissible limits of inhalation product specification for delivered dose uniformity and fine particle mass. The results that do not meet the requirements of the Pharmacopoeia of the Union should be rationalized.

33. The doses between the last dose indicated in the inhalation product information and the last container exhaustion dose should also be tested for delivered dose uniformity and fine particle mass, and information on the exhaustion (decreasing) profile should be provided where applicable. At least three containers from two different batches should be investigated. This testing may be waived if the container contains a lockout mechanism that prevents dosing actuation beyond the number of doses specified in the inhalation product information.

Fine particle mass and delivered dose uniformity over patient flow rate range (CTD 3.2.P.2.4)

34. A test should be conducted to demonstrate the consistency of the minimum delivered dose and the fine particle mass over the range of flow rates (through the delivery device) achievable by the intended patient population, at constant volume. The minimum (e.g., 10th percentile), median, and maximum (e.g., 90th percentile) achievable rate should be investigated. The range of flow rates should be rationalized in relation to clinical findings and published data for the same delivery device.

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

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

36. For inhalation products that may be administered with a spacer or holding chamber, a study should be conducted to determine to determine the effect of their use on the fine particle mass. If product instructions for the spacer or holding chamber include an in-use cleaning schedule (e.g., weekly cleaning), the

test for determination of fine particle mass should be conducted before and after cleaning the spacer or holding chamber. The procedure for determination of fine particle mass used for routine testing of the product may be modified to simulate the use of a spacer or holding chamber by the patient (e.g., a 2 second delay, tidal breathing). Any differences in fine particle mass should be assessed for their clinical relevance using all clinical data obtained in relation to the spacer or holding chamber.

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

37. The fine particle mass should be routinely determined using the minimum recommended dose (if technically possible). If the fine particle mass test included in the inhalation product specification uses a sample volume greater than the minimum recommended dose, a study should be conducted to demonstrate that the sample volume used routinely provides results equivalent to those obtained using the minimum recommended dose. The rationale for not conducting this test (e.g., for low dosed inhalation products) and for non-equivalent results should be provided.

38. The fine particle mass of one dose should be determined according to the method of determination specified in the inhalation product specification, modified only as necessary to accommodate the reduced sample volume. Stage pooling prior to analysis is acceptable. The selection of the pooled stages should be rationalized. If this study is not feasible due to the sensitivity of the analytical method, the rationale supporting failure to conduct it should be provided.

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

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

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

41. Using a multistage impactor or impinger, the mass of active substance on each stage and the cumulative mass that are less than this stage should be determined. At the same time, determination of the percentage of delivered dose or other derived parameter is not advised as these can hide variations in delivered dose. As a rule, a dependency diagram of cumulative percentage of particles (droplets) less than a cut-off diameter versus each stated cut-off diameter should usually be provided. From this, the mass median aerodynamic diameter and geometric standard deviation may be determined, if appropriate (in case of unimodal log-normal distribution). Mass balance correction should also be considered.

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

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

Actuator (mouthpiece) and other inhaler components deposition (CTD 3.2.P.2.4)

44. The amount of active substance deposited on the actuator and mouthpiece as well as (where applicable) on other parts of the inhaler should be determined and, where applicable, demonstrated to be consistent with any correction factor used for the rationale of ex-valve active substance content (ex-delivery device) specified in the inhalation product information.

Total active substance quantity delivered
and active substance delivery rate
(CTD 3.2.P.2.4)

45. To allow an assessment of the complete delivery profile of the inhalation product used in in vivo (pivotal and/or comparative clinical studies), the total active substance delivered (i.e. total dose delivered to the patient) and active substance delivery rate results should be provided for the batches used in these studies. A validated method (e.g., breath simulator) should be used. The aerosol should be generated with the same nebulizer system(s) and conditions as used for in vivo studies.

Shaking requirements
(CTD 3.2.P.2.4)

46. For inhalation products requiring shaking before use (in accordance with the inhalation product information), it is necessary to confirm the accuracy of the shaking instructions provided to the consumer. The possibility of foaming and inaccurate dose release caused by excessive shaking should be examined by determining the delivered dose uniformity.

Initial and re-pumping requirements
(CTD 3.2.P.2.4)

47. When studying primary pumping, a study should be conducted to rationalize the number of actuations specified in the inhalation product information, which should be fired to waste (pumping actuations) before the consumer uses the inhalation product for the first time. Containers should be stored in various orientations prior to the initiation of the study in order to determine the effect of orientation. The length of storage should be indicated and rationalized prior to conducting the study.

48. When studying re-pumping, the number of pumping actuations required until the subsequent doses meet the inhalation product specification limits for delivered dose uniformity should be determined.

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

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

50. A test should be conducted to rationalize the length of time that the product may be stored without use (after initial pumping) before re-pumping in accordance with the recommendations given in the inhalation product information, as well as the number of re-pumping actuations required. Containers should be stored in various orientations prior the study in order to determine the effect of orientation. Test of inhalation products at different stages through container life should also be considered. Multiple points should be used. The number of re-pumping actuations required until the subsequent doses meet the inhalation product specification limits for delivered dose uniformity should be determined. Re-pumping instructions, including any instructions on storage orientation, should be provided to the health care professional and the consumer.

Cleaning requirements (CTD 3.2.P.2.4)

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

Low temperature performance
(CTD 3.2.P.2.4)

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

53. The number of actuations required until the subsequent doses meet the medicinal product specification limits for delivered dose uniformity and fine particle mass should be determined. If the inhalation product fails the test (e.g., re-pumping actuations required exceed the number required according to the inhalation product information), an additional test should be conducted to determine the method and length of time needed to adequately warm the containers so that satisfactory performance of the inhalation product is achieved.

54. Information regarding low temperature use of the inhalation product should be provided to the health care professional and the consumer. If this test is not conducted, information on the method and duration of warming the container should be provided to the health care professional and the consumer. Alternative approaches for inhalation products that do not tolerate low temperatures should be fully rationalized.

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

55. A test should be conducted to determine the effect of temperature cycling on the performance of the inhalation product. Containers should be stored in various orientations and cycled between recommended storage conditions and a temperature below freezing (0 °C).

56. For suspensions, cycling between the recommended storage conditions and a high temperature storage (e.g., 40 °C) should be considered, and may be carried out together with the low temperature cycling study. Storage time should be

at least 24 hours under each condition. Containers should be stored under each condition at least five times.

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

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

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

Robustness (CTD 3.2.P.2.4)

59. The inhalation product performance should be investigated under conditions simulating their use by patients. This includes activating the delivery device at the frequency indicated in the inhalation product information.

60. In determining robustness, studying the effect of transferring a delivery device during the use to another container and studying the effect of a drop delivery device simulating, as well as determining the robustness of the lockout mechanism (if any) should be considered.

61. Vibrational stability of powder mixtures should be demonstrated in transportation and use. Significant variations in the delivered dose and (or) fine particle mass should be fully considered in terms of the safety and efficacy of the inhalation product.

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

62. The development of the delivery device should be described. Any changes implemented in the design (e.g., change of component materials) and (or) manufacturing process of the delivery device (e.g., scale up from single cavity to multiple cavity device) during the development should be considered in terms of the impact on the inhalation product performance characteristics (e.g., delivered dose, fine particle mass). If prototype delivery devices were used in clinical studies, appropriate data should be provided to demonstrate the equivalence of the prototype(s) with the inhalation product being released into circulation in the territories of the Member States.

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

64. For breath-operated (breath-activated) delivery devices, data should be provided to demonstrate that all target patient groups are capable of triggering the delivery device. This could be evaluated as part of the clinical program during patient delivery device use studies. The triggering mechanism should be well characterized as part of the delivery device development program.

65. Each device-metered dry powder inhaler should have a counter or other filling indicator to give the patient indication of when the number of actuations indicated in the inhalation product information has been achieved. Inclusion of dose counters is also recommended for other multiple dose inhalation products.

Preservative efficiency
(CTD 3.2.P.2.5)

66. For inhalation products containing a preservative, a test should be conducted to demonstrate the efficiency of the preservative.

Compatibility
(CTD 3.2.P.2.6)

67. If the inhalation product is to be diluted prior to administration, compatibility should be demonstrated with all diluents over the range of dilution proposed in the inhalation product information. These studies should also be conducted on aged samples, and should cover the duration of storage (shelf life) of the diluted product indicated in the inhalation product information. If, according to the inhalation product information, co-administration with other medicinal products is allowed, compatibility should be demonstrated with respect to medicinal products for treatment of the underlying disease as well as to co-administered medicinal products.

68. Tests for parameters such as pH, droplet size distribution, inhalation product output rate from the delivery device and total inhalation product output from the delivery device should be carried out, precipitation possibility should be assessed. Differences from the original inhalation product should be assessed in terms of their significance.

2. Nasal products

69. The tests indicated in Table 2 are normally conducted to characterize nasal products. At the same time, different types of nasal products require different tests.

Table 2

Pharmaceutical development studies for nasal products

Pharmaceutical development studies	Pressurised metered dose nasal sprays	Nasal powders (device-metered)	Nasal liquids				
			single use drops	multiple use drops	single use sprays	multiple use metered dose sprays	non-metered dose sprays
Physical	yes[1]	yes	yes[1]	yes[1]	yes[1]	yes[1]	yes[1]

Pharmaceutical development studies	Pressurised metered dose nasal sprays	Nasal powders (device-metered)	Nasal liquids				
			single use drops	multiple use drops	single use sprays	multiple use metered dose sprays	non-metered dose sprays
characterization							
Minimum fill rationale	yes	yes	yes	yes	yes	yes	yes
Extractables and leachables	yes	no	yes	yes	yes	yes	yes
Delivered dose uniformity through container life	yes	yes	no	no	no	yes	no
Particle (droplet) size distribution	yes	yes	no	no	yes	yes	yes
Actuator (mouthpiece)	yes	yes	no	no	yes	yes	yes
Shaking requirements	yes[1]	no	yes[1]	yes[1]	yes[1]	yes[1]	yes[1]
Initial and re-pumping requirements	yes	no	no	no	yes	yes	yes
Cleaning requirements	yes	yes	no	yes	no	yes	yes
Low temperature performance	yes	no	no	no	no	no	no
Performance after temperature cycling	yes	no	no	no	yes	yes	yes
Effect of environmental moisture	yes	yes	no	no	no	no	no
Robustness	yes	yes	yes	yes	yes	yes	yes
Delivery device development	yes	yes	yes	yes	yes	yes	yes
Preservative	no	no	yes[2]	yes[2]	yes[2]	yes[2]	yes[2]

Pharmaceutical development studies	Pressurised metered dose nasal sprays	Nasal powders (device-metered)	Nasal liquids				
			single use drops	multiple use drops	single use sprays	multiple use metered dose sprays	non-metered dose sprays
efficiency							
Package contents output determination	no	no	no	no	no	no	yes

[1] For suspensions.
[2] If a preservative is present.

70. The pharmaceutical development studies should be performed in accordance with Section IV of these Guidelines, with the exception of tests for fine particle mass.

71. With regard to particle (droplet) size distribution, full characterization of the nasal product should be provided. It should be demonstrated that deposition of the nasal product is localized in the nasal cavity (e.g., by demonstrating that the majority of the particles (droplets) are larger than 10 microns).

V. Medicinal product manufacture

72. To fully characterize a medicinal product, the formulation should include the concentration of the active substance in the finished product, the nominal amount, and the target delivery amount.

73. The manufacturing process of the medicinal product, including all filling and packaging operations, should be described for each dose strength and each container closure system (including varying in the number of actuations).

74. The manufacturing process for the medicinal product should be validated to ensure the homogeneity of the formulation throughout the filling process during routine production and include controls of appropriate fill volume or fill weight range, and correct applying of closure system (e.g., crimp dimensions of the

aerosol container, spray device, as well as leak testing for pressurised products, blister sealing for dry powder inhalers, torque measurement for screw thread pumps).

75. The medicinal product should also have an internal process control for performance testing of the actuation release mechanism (e.g., weight of actuated dose) of each product unit (where appropriate).

76. If equilibration time is provided for pressurised products before release testing, it should be specified and rationalized along with other aspects of the manufacturing process.

VI. Excipients

77. Besides the usual pharmacopoeial requirements, additional tests to characterize the material used should be included in the specification. For dry powder inhalers, such tests include a performance test for the excipients and suitable multi-point particle size test for the excipient(s) (e.g., lactose) or granules size test for excipients and (or) active substance. Acceptance criteria for these tests should be established by the results of batches analysis used to manufacture medicinal product for in vivo (pivotal and (or) comparative clinical) studies, although in vitro test data obtained with a cascade impactor (impinger) may be sufficient to demonstrate the suitability of the acceptance criteria.

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

79. In addition, it is advised to consider control of microbiological purity of excipients used, and where applicable, provide the rationale for not conducting routine tests for microbiological purity.

1. Pharmacopoeial excipients

80. Well-studied excipients used in the formulations are tested in accordance with the Pharmacopoeia of the Union or Pharmacopoeias of the Member States. They may be used without providing safety data on the excipient alone, if the amounts used are standard for the route of administration. Any excipient in the formulation that is not well-studied must be demonstrated to be safe when administered by the new route of administration and may be considered jointly with the competent authority of the Member State.

2. Excipients not included in the Pharmacopoeia of the Union (Pharmacopoeias of the Member States)

81. Excipients, the quality of which is not regulated by pharmacopoeial monograph, must be safe when administered by the inhalation or nasal route of administration. Tests and acceptance criteria to be included in the excipient specification, particularly with respect to purity, should be established based on results of the analysis of batches used in safety studies. In addition to the specification, information on the manufacturer of the excipient, which should be agreed in advance with the Member States' competent authorities, may also be necessary.

VII. Medicinal product specification(s)

82. This section contains information on product-specific tests to be included in the specification. Standard medicinal product specification tests (e.g., identification, test for presence of product-related impurities, degradation products, active substance assay, and pH) have not been included in this section, but these tests should be included in the specification. Other regulations that are part of the

Union's law or the Member States' legislation in the field of medicinal product circulation should be used for guidance in this regard.

83. Acceptance criteria should be set based on the actual ranges of variation in batches that showed acceptable performance in vivo, as well as the intended use of the medicinal product.

84. Considering stability studies data and the possibility of the influence of the manufacturing process is also advisable. In addition, there may be different limits at the time of the release of the medicinal product and at the end of its duration of storage (shelf life), which must be described and rationale. Requirements to Stability Studies of Medicinal Products and Pharmaceutical Substances approved by Decision No. 69 of the Eurasian Economic Commission's Board dated May 10, 2018 should be considered when drawing up specifications, conducting tests at the time of the release and at the end of duration of storage (shelf life) of the medicinal product as well as in periodic testing.

1. Inhalation products

85. The list of tests to be included in the specification for inhalation products is given in Table 3. However, not every type of inhalation products requires conducting all test types.

Table 3

Tests to be included in the specification for inhalation products

Tests to be included in the specification for inhalation products	Pressurised metered dose inhalers	Dry powder inhalers		Products for nebulization		Non-pressurised metered dose inhalers
		with a dosage device	pre-metered	single-dose	multidose	
Description	yes	yes	yes	yes	yes	yes
Assay	yes	yes	yes	yes	yes	yes
Moisture content	yes[1]	yes	yes	no	no	yes[1]
Mean delivered dose	yes	yes	yes	no	no	yes

Delivered dose uniformity	yes	yes	yes	no	no	yes
Uniformity of dosage units	no	no	yes	yes	no	no
Fine particle mass	yes	yes	yes	yes[2]	yes[2]	yes
Leak rate (integrity)	yes	no	no	no	no	no
Microbiological purity	yes	yes	yes	yes	yes	yes
Sterility	yes[3]	yes[3]	yes[3]	yes[3]	yes[3]	yes[3]
Leachables	yes	no	no	yes	yes	yes
Preservative content	no	no	no	yes[4]	yes[4]	yes[4]
Number of actuations (doses) per container	yes	yes	no	no	no	yes

[1] May be excluded if the moisture content does not affect the inhalation product characteristics.
[2] For suspensions, with testing on nebulizers provided in the inhalation product information unless otherwise indicated.
[3] If the inhalation product is sterile.
[4] If a preservative is present.

Description

86. A description of both the finished product and the full delivery device (e.g., including actuator) should be given where applicable. For products for nebulization, the primary packaging should be described (e.g., transparent LDPE container).

Assay

87. The amount of active substance should be determined for inhalation products per dose unit, per weight unit or per volume unit. For single dose inhalation products, the amount of active substance should be expressed per 1 dose. In respect of inhalation products, acceptable standard assay norms specified in the Pharmacopoeia of the Union or Pharmacopoeias of the Member States are applied.

Moisture content

88. The limit for moisture content should be established based on results of stability studies. If the results are stable throughout the shelf life of the inhalation product, or if any changes in moisture content do not result in changes to any other parameters, the test may be excluded from the specification.

Mean delivered dose

89. The amount of active substance in one delivered dose should also be determined by calculating the mean of the delivered dose uniformity test results, with corrections as necessary to convert from “per dose” amounts to “per actuation” amounts. Permissible limits are ± 15% of the labeled value.

Delivered dose uniformity

90. The delivered dose uniformity test should be conducted in accordance with the method prescribed by the Pharmacopoeia of the Union or Pharmacopoeias of the Member States or a suitably validated alternative. Applied limits of the delivered dose uniformity should be consistent with the Pharmacopoeia of the Union or Pharmacopoeias of the Member States, or requirements for tolerance levels of results of determination of variability of uniformity of delivered doses for each delivery device separately and between delivery devices.

91. For solution finished dosage forms, it is allowed to use the weight uniformity of the delivered doses instead of the content uniformity of the delivered doses for the rationale.

Uniformity of dosage units (content uniformity)

92. Content uniformity should be investigated on samples obtained from containers according to the inhalation product information. Acceptance limits should be rationalized, taking into consideration the requirements of the Pharmacopoeia of the Union or Pharmacopoeias of the Member States.

93. For solution finished dosage forms, it is allowed to carry out the test for the weight uniformity of the delivered doses instead of the test for the content uniformity of the delivered doses for the rationale.

Fine particle mass

94. The fine particle mass determination should be conducted using a validated method based on the multistage impactor or impinger, or a validated alternative method. It is generally considered acceptable to set upper and lower limits on the results of pooled stages by particle size less than 5 μm in diameter distribution, although alternative limits are acceptable with adequate rationale. It is preferable to determine the mass of the active substance rather than the percentage of emitted dose (or other derived parameter). Additional criteria such as grouped stages or limits for mass median aerodynamic diameter and (or) geometric standard deviation are advisable to use if the fine particle mass is insufficient to fully characterize the particle size distribution of the therapeutic dose. In case the significance of the particle mass exceeds 5 μm in diameter, for the therapeutic index of the inhalation product, the control of the particle size distribution above 5 μm in diameter may be necessary.

95. Limits should be set for the delivered and for the main dose in accordance with the fine particle mass for inhalation product batches used for in vivo pivotal and (or) comparative clinical studies.

Leak rate (integrity)

96. A leak rate (integrity) test and limits should be included in the specification.

Microbiological purity

97. Microbiological purity testing should be conducted in accordance with the method prescribed by the Pharmacopoeia of the Union or Pharmacopoeias of the Member States.

Sterility

98. Sterility testing should be conducted in accordance with the method prescribed by the Pharmacopoeia of the Union or Pharmacopoeias of the Member States.

Extractables and leachables

99. Depending on the results of the pharmaceutical development study on extractables and leachables, and, in particular, on the results of safety assessments, the decision is made on inclusion or non-inclusion of the test and the qualified limits for extractables and leachables in the specification.

Preservative content

100. Quantification of the preservative should be conducted.

Number of actuations (doses) per container

101. The number of actuations per container should be demonstrated to be no less than the number of actuations specified in the inhalation product information.

2. Nasal products

102. A list of tests, the information on which shall be included in the specification for nasal products, is specified in Table 4. However, not every type of nasal products requires conducting all test types. The tests should be performed in

accordance with the descriptions given in paragraphs 82 to 101 of these Guidelines supplemented by a test for particle (droplet) size distribution, if applicable.

Table 4

Tests to be included in the specification for nasal products

Tests to be included in the specification for nasal product	Pressurised metered dose nasal sprays	Nasal powders (device-metered)	Nasal liquids				
			single use drops	multiple use drops	single use sprays	multiple use metered dose sprays	multiple use non-metered dose sprays
Description	yes	yes	yes	yes	yes	yes	yes
Assay	yes	yes	yes	yes	yes	yes	yes
Moisture content	yes	yes	no	no	no	no	no
Mean delivered dose	yes	yes	no	yes	no	yes	no
Delivered dose uniformity	yes	yes	no	yes	no	yes	no
Uniformity of dosage units	no	no	yes	no	yes	no	no
Leak rate (integrity)	yes	no	no	no	no	no	no
Microbiological purity	yes	yes	yes	yes	yes	yes	yes
Sterility	yes[1]	yes[1]	yes[1]	yes[1]	yes[1]	yes[1]	yes[1]
Preservative content	no	no	yes[2]	yes[2]	yes[2]	yes[2]	yes[2]
Number of actuations (doses)	yes	yes	no	no	no	yes	no
Particle (droplet) size distribution	yes	yes	no	no	yes	yes	yes
Percentage of output of the package contents	no	no	no	no	no	no	yes
Package contents volume	no	no	yes	yes	no	no	no

[1] If the product is sterile.
[2] If a preservative is present.

Particle (droplet) size distribution

103. Testing should be conducted using a validated method (e.g., cascade impaction or, for solutions, laser diffraction). The limits are required for an allowed range for the median diameter of particles (droplets) and particles (droplets) up to 10 μm in size. Acceptable limits for the median diameter particles (droplets) and particles (droplets) up to 10 μm in size should be qualified by results for batches used in in vivo (pivotal clinical and/or comparative) studies.

VIII. Medicinal product container closure system

104. In addition to standard container closure system tests included in specification, the specifications should include additional tests to confirm reproducibility of active substance delivery by the delivery device (where applicable). For example, for pressurised metered dose inhalers or pressurised metered dose nasal sprays, specifications should include tests such as individual delivered dose weight for sprays, as well as information on the length and diameter of the actuator orifice.

105. The composition of all container closure system components should be provided and should comply with certain standards (including the Pharmacopoeia of the Union or Pharmacopoeias of the Member States) in relation to their intended use.

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

107. For non-pharmacopoeial components, in addition to the polymer used, any other additives should also be described.

IX. Delivery devices, including spacers and holding chambers

108. For all delivery devices, it is necessary to submit data that support the information provided in the summary of product characteristics for inhalation and

nasal products and patient information leaflet in relation to the shelf life of the device (before and during use), storage conditions (where relevant) and the number of refills permitted (if applicable).

109. If a spacer or holding chamber is required for administration of the product to a particular group of patients (e.g., administration of high dose steroids in a pediatric population), its use should be validated.

110. Relevant information on the spacer or holding chamber should be given in the Summary of Product Characteristics.

111. The suitability of the spacer should be supported by in vitro tests and clinical studies. Besides, any effects caused by device use (e.g., reduced amount of large particles) should be supported by in vitro test data.

X. Product stability

112. Medicinal product stability tests should be carried out in accordance with the Requirements for the study of the stability of medicinal products and pharmaceutical substances. Weight loss should also be monitored where appropriate.

113. If product performance is influenced by the storage orientation (e.g., pressurised metered dose inhaler), 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.

114. If the medicinal products includes secondary packaging in order to protect it from light and (or) humidity (e.g., dry powder inhaler inside a foil overwrap), the length of time that the medicinal product may be used after the protective packaging has been removed should be supported by stability study results. The studies should involve removing the medicinal product from the protective packaging close to the end of its shelf life and testing it after the exposure in accordance with specification. For example, if a medicinal product should be used within three months after removal of the protective packaging (according to the inhalation product information), it 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.

115. Information on the medicinal product use after its extraction from the protective packaging should be provided to the consumer.

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APPENDIX No. 1
to the Guidelines on the quality
of inhalation and nasal products

REQUIREMENTS
for studies on the pharmaceutical development of generic products for inhalation and nasal products

I. General provisions

1. These Requirements define the features of studies on the pharmaceutical development of generic products for inhalation and nasal products (hereinafter referred to as products).

2. Generic products should be similar to the original (reference) product. Therapeutic equivalence with respect to the original (reference) medicinal product should be confirmed by the results of in vitro and (or) in vivo studies in accordance with the Guidelines on the preparation of clinical documentation (research, demonstration of therapeutic equivalence) for inhaled medicinal products used for the treatment of asthma in adults, adolescents and children and chronic obstructive pulmonary disease in adults, approved by the Eurasian Economic Commission. In all cases, the comparability of the generic and original (reference) product must be confirmed under in vitro test conditions in accordance with these Requirements.

II. Inhalation products

3. For pressurised metered dose inhalers, dry powder inhalers, and metered dose nebulizers, it is necessary to provide in vitro test data on the generic product for inhalation (hereinafter referred to as product for inhalation) versus the original (reference) product for inhalation, on the complete profile of particle size distribution on an individual cascade using a cascade impactor (impinger). If there is a flow rate dependency, a range of flow rates should be tested. In addition, the

delivered dose should be compared. For products for nebulization, the complete droplet size distribution of the generic product for inhalation should be compared with the original (reference) product for inhalation using a validated method, such as laser diffraction. In addition, the output rate and total active substance output should be compared. If applicable, the aerosol should be obtained with the nebulizer systems in vivo.

For generic solutions for nebulization having the same qualitative and quantitative composition in relation to the original inhalation product, comparisons may be waived.

For suspensions for nebulization, the particle size distribution on individual cascades should also be compared.

If any differences beyond normal analytical variability are detected, the rationale as to that the differences will not result in different deposition and (or) absorption characteristics should be provided.

4. For batches used in vivo, limited or no data may be available. In this regard, the following explanations in relation to certain inhalation product pharmaceutical development sections and the excipient section are given:

a) delivered dose uniformity and fine particle mass within flow ranges created by the patient, – if no in vivo studies were performed, the range of flow rates investigated should be rationalized;

b) particle (droplet) size distribution – if no in vivo studies were conducted, the results of batches analysis, reflecting the commercial process (e.g. in terms of batch size, manufacturing method of the inhalation product and the device) should be compared with the batches used for the rationale of in vitro equivalence;

c) active substance delivery rate and total quantity delivered – if no in vivo studies were conducted, the results of batches analysis, reflecting the commercial process should be compared with the batches used for the rationale of in vitro equivalence;

d) pharmacopoeial excipients – if no in vivo studies were conducted, any limits for relevant parameters (such as particle size distribution and shape of the

carrier for dry powder products) must be based on the batches used for the rationale of in vitro equivalence;

e) extractables and leachables – safety assessment may also be based on comparative profile of the generic product versus the original (reference) inhalation product, if this is rationalized by the composition of packaging.

III. Nasal products

5. For generic nasal products (hereinafter referred to as nasal products), which should be similar to the original nasal product, studies required to demonstrate therapeutic equivalence may depend on the pharmacological effect (local or systemic). The studies are conducted in accordance with the Rules for Conducting Bioequivalence Studies of Medicinal Products within the Eurasian Economic Union, approved by Decision No. 85 of the Eurasian Economic Commission's Council dated November 3, 2016, and the Guidelines on Pharmacokinetic and Clinical Studies of the Bioequivalence of Modified-release Products, Bioequivalence of Liposomal Products, Bioequivalence of Corticosteroids for Topical Use in Dermatology, approved by the Eurasian Economic Commission.

6. For nasal sprays, complete comparative data of the generic product versus the original nasal product must be provided with respect to the droplet size distribution using a validated method, such as laser diffraction. In addition, the delivered dose for nasal sprays and nasal powders should be compared.

For nasal drops, the results of comparing the droplet volume of the generic product versus the original (reference) nasal product should be provided.

If any differences beyond normal analytical variability are detected, the rationale as to that the differences will not result in different deposition and (or) absorption characteristics should be provided.

7. For batches used in vivo, limited or no data may be available. The provisions of paragraph 4 of these Requirements shall apply to the extractables and leachables, the droplet size distribution and the excipients used.

APPENDIX No. 2
to the Guidelines on the quality
of inhalation and nasal products

REQUIREMENTS
for information intended for consumers and health care professionals

I. General provisions

1. These Requirements establish the features for inclusion the information specific to inhalation and nasal products in the Summary of Product Characteristics. In these Requirements, the information that should be included in the Summary of Product Characteristics is given in accordance with the structure of the Summary of Product Characteristics, approved by Decision No. 88 of the Eurasian Economic Commission's Council dated November 3, 2016 On Approval of the Requirements for the Medication Guide and Summary of Product Characteristics of Medicinal Products for Human Use" (hereinafter referred to as the Summary of Product Characteristics).

II. Inhalation products

1. Qualitative and quantitative composition (Section 2 of the Summary of Product Characteristics)

2. For pressurised metered dose inhalers, dry powder inhalers, and metered dose nebulizers, the content of actuated active substance can be expressed as the output from the dispenser (measured dose) or the output from the nebulizer (target delivered dose).

3. For all inhalation products containing new active substances and products containing known active substances used in the composition of inhalation products for the first time, the delivered dose or an alternative characteristic (e.g. fine particle mass) should be labeled if the alternative characteristic is agreed upon with

the authorized authorities of the Eurasian Economic Union Member States (hereinafter referred to as the Member States).

4. For authorized inhalation products, current practice of each Member State should be followed. In any case, it should be clearly stated whether the labeled content corresponds to the metered dose (ex valve), to the delivered dose (ex actuator), or to the agreed alternative characteristic.

2. Posology and method of administration (Section 4.2 of the Summary of Product Characteristics)

5. Since different inhalation products containing the same active substance might be labeled with the same metered or target delivered dose but have a different therapeutic effect due to differences in the fine particle mass content compared to the fine particle mass content in the original (reference) inhalation product, it should be clearly stated if the inhalation product is not interchangeable with other medicinal products.

6. The following data should be clearly described in the inhalation product information (if applicable):

a) shaking requirements;

b) the use at low temperatures;

c) the need for pumping and re-pumping;

d) the effect of flow rate on the product's performance;

e) the orientation of the inhaler during inhalation;

f) the use of any specific spacer (holding chamber);

g) cleaning requirements, including instructions for any specific spacer (holding chamber).

7. For products for nebulization, the nebulizer system (nebulizer systems) and settings that were proven effective and safe in vivo, including information on the droplet size distribution, active substance delivery rate and target total delivered content of active substance should be indicated.

3. Special precautions for storage
(Section 6.4 of the Summary of Product Characteristics)

8. For pressurized metered dose inhalers, the following data should be included in the product information: "The canister contains a pressurised liquid. Do not expose to temperatures higher than 50 °C. Do not pierce the canister."

III. Nasal products

1. Qualitative and quantitative composition
(Section 2 of the Summary of Product Characteristics)

9. For pressurised metered dose nasal sprays, metered dose nasal sprays, and nasal powders the content of actuated active substance can be expressed as the content to be actuated from valve (metered dose) or as the content to be actuated from actuator (target delivered dose).

10. For all nasal products containing new active substances and nasal products containing known active substances used for the first time in nasal products, the delivered dose should be labeled.

11. For authorized nasal products, current practice of each Member State should be followed. In any case, it should be clearly stated whether the labeled content corresponds to the metered dose (ex-valve) or to the delivered dose (ex-actuator).

12. For nasal drops, the content of active substance per drop should be labeled.

2. Posology and method of administration
(Section 4.2 of the Summary of Product Characteristics)

13. The following data should be clearly described in the nasal product information (if applicable):

a) shaking requirements;

b) the use at low temperatures;

c) the need for pumping and re-pumping;

d) cleaning requirements.

3. Special precautions for storage
(Section 6.4. of the Summary of Product Characteristics)

14. For pressurised metered dose nasal sprays, the following data should be included in the product information: "The canister contains a pressurised liquid. Do not expose to temperatures higher than 50 °C. Do not pierce the canister."

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