ANNEX

to the Recommendation of the Board
of the Eurasian Economic Commission
dated 20 No.

GUIDELINES
on the preparation of clinical documentation (research, demonstration of therapeutic equivalence) for orally inhaled medicinal products used for the treatment of asthma in adults, adolescents and children and chronic obstructive pulmonary disease in adults

I. General provisions

1. These Guidelines cover the general requirements for clinical documentation for inhalation products, approaches to demonstration of therapeutic equivalence between two orally inhaled medicinal products containing a single active substance or combination medications used in management and treatment of bronchial asthma in adults, adolescents and children, and chronic obstructive pulmonary disease in adults.

2. These Guidelines describe the requirements for clinical trials of orally inhaled medicinal products used for the treatment of asthma in adults, adolescents and children and chronic obstructive pulmonary disease in adults (hereinafter referred to as inhaled products). These Guidelines are related to all documents on the diagnosis, therapy and management of bronchial asthma of the Member States of the Eurasian Economic Union (hereinafter referred to as the Member States), as well as documents affecting the conduct of clinical trials of medicinal products of the Eurasian Economic Commission (hereinafter referred to as the Commission).

3. The purpose of these Guidelines is to describe the principles and approaches to the conduct of clinical trials for the demonstration of

therapeutic equivalence between two inhaled products used for management and treatment of adult patients suffering from bronchial asthma and/or chronic obstructive pulmonary disease, as well as children and adolescents suffering from bronchial asthma.

4. These Guidelines provide instructions on the preparation of clinical documentation based on the characteristics of the device, from which the active substance is inhaled. However, these Guidelines do not address other issues of preparation of clinical documentation for inhaled product.

5. Knowledge of the *in vitro* performance, and particularly the flow-dependent particle size distribution of the product, is important and will have some influence on the clinical development program.

6. These Guidelines are relevant for the inhaled products, which can be classified into the following groups:

a) pressurized metered dose inhalers:

non-breath-operated pressurized metered dose inhalers;

breath-operated metered dose inhalers;

pressurized metered dose inhalers with spacers or holding chambers;

b) non-pressurized metered dose inhalers:

dry powder inhalers using a reservoir and metering mechanism;

dry powder inhalers using a pre-dispensed dose;

c) non-metered-dose inhalers:

solutions and suspensions for nebulization.

II. Definitions

7. For the purposes of these Guidelines, in addition to the terms established by the Rules for Conducting Bioequivalence Studies of Drug Products on the Territory of the Eurasian Economic Union approved by the Decision of the Council of the Eurasian Economic Commission No. 85 dated

November 3, 2016 and the Guidelines for the Quality of Drug Products for Inhalations and Nasal Drugs to be approved by the Commission, the terms with the following meanings are used:

«sensitivity analysis» means a method of assessing the ability to identify the expected difference between effective treatment and less effective or ineffective treatment based on a clinical trial;

«delivered dose» means the amount of the active substance of the drug, that the patient receives with the dose exiting from the mouthpiece of the inhalation device;

«single dose study» means a study of the effect of administration of a single dose of each drug in a clinical trial;

«knemometry» means measurement of the growth rate of the lower leg bone;

«pulmonary deposition» means the amount of active substance deposited in the airways (except of the mouth and throat);

«dose linearity» means a representation of the dependence of the drug effect on the dose described by $f(x) = ax + b$ function, where a and b are numerical constants;

«onset of action (for the forced expiratory volume in one second (FEV_1))» means forced expiratory volume improvement for a certain period of time expressed in absolute or relative units in one of the following ways:

FEV_1 improvement of 200 ml from baseline;

time from the moment of inhalation and up to 50% of the maximal response of the FEV_1 measurement to inhalation;

the percentage of the maximum response of the FEV_1 measurement achieved within a given time (5 or 10 minutes from the initial level of FEV_1), if the maximum FEV_1 improvement in a patient is at least 15%;

«relative potency» means the potency of the study drug against the reference drug. It is defined as the dose of the study drug, that produces the same biological response per dosage unit of the reference drug (comparative results for various doses);

«duration of effect» means the time, for which FEV_1 (or another measured parameter) returns to its original value for no less than 80-90% of the peak effect;

«therapeutic equivalence» means the absence of clinically relevant differences in the efficacy and safety profile of the study drug and the reference drug;

«breath-operated inhalers» means breath-triggered metered dose inhalers, for which a patient needs to generate a minimum airflow value in order for the inhaler to release the aerosol.

III. General requirements for the assessment of inhalation devices and research types

8. Pressurized and non-pressurized metered dose inhalers, dry powder inhalers and nebulizers have different flow-dependent pulmonary deposition patterns. Patient preference in the handling of these devices differs. Some general requirements for their *in vitro* assessment and clinical documentation are given below.

1. Pressurized metered dose inhalers

Non-breath-operated pressurized metered dose inhalers

9. Non-breath-operated pressurized metered dose inhalers (pMDIs) contain different propellants and other excipients, and may use different delivery systems, all of which may result in differing clinical outcomes. The standard non-breath-operated pressurized metered dose inhaler requires

coordination of actuation of the device with inspiration of breath; breath-operated devices and the use of spacers with non-breath-operated pressurized metered dose inhalers reduce the need for such coordination. Spacers are required to be available for use with all non-breath-operated pressurized metered dose inhalers. If the inhaled product is intended for the pediatric population, then availability of simultaneous use of spacer must be considered during the pharmaceutical development. Appropriate data to support the use of a specific named spacer with a non-breath-operated pressurized metered dose inhaler containing a specific active substance or specific combination of active substances must be included in the registration dossier of the inhaled product.

Breath-operated metered dose inhalers

10. A minimal peak inspiratory flow (PIF) is required to trigger a breath-operated inhaler (BOI). If this minimal peak inspiratory flow cannot be achieved by the patient, inhaler use will be unsuccessful. Therefore, the clinical program must include relevant data regarding the minimal peak inspiratory flow required to trigger the breath-operated inhaler (this data may be generated using a placebo inhaler device) and description of those patient groups who would normally be able to produce a sufficient minimal peak inspiratory flow to trigger the device and those patient groups who may have problems (for example, patients with severe airflow obstruction, patients suffering from an acute attack of asthma, small children, etc.). The relevant patient population must be adequately investigated and clearly defined in order, that the product has been used by suitable patient groups only for the indications. The reference product for a breath-operated inhaler can be the corresponding non-breath-operated pressurized metered dose inhaler.

11. If inhalers have two methods of actuation – hand-operated and breath-operated – then patients using these inhalers need special explanation of their method of application in the basic prescribing information (package leaflet). These inhalers need explanations in the basic prescribing information (package leaflet) as to how to recognize an inadequate hand-operated or breath-operated inhalation and as to when they may need to be switched from one method of actuation to the other. These two modes of inhaler actuation should be compared using the parameters outlined in Section IV of these Guidelines to determine whether there is a need for separate clinical data to support each method of inhalation.

Spacers and holding chambers

12. Effective spacers facilitate inhalation via a non-breath-operated pressurized metered dose inhaler and decrease the amount of medicinal product deposited in the mouth and pharynx and subsequently swallowed. The use of a spacer is recommended for all patients, but particularly for those who find coordination of actuation of the non-breath-operated pressurized metered dose inhaler with inspiration of breath difficult (for example, children and the elderly) and for patients treated with inhaled glucocorticosteroids (IGCS).

13. Spacers usually increase pulmonary deposition. However, a specific spacer may perform differently with different active substances and similarly, a specific active substance in a specific non-breath-operated pressurized metered dose inhaler may have different deposition, if inhaled through spacers with different performance data. The distribution of the active substance in the respiratory tract and patient's clinical response to an active substance cannot be assumed to be equivalent, if a different spacer is used, or if a different non-breath-operated pressurized metered dose inhaler is used

with the same spacer. The development of a non-breath-operated pressurized metered dose inhaler should always include the testing of at least one specific named spacer for use with the particular non-breath-operated pressurized metered dose inhaler containing a particular active substance. This spacer has to be appropriate for the intended patient population.

14. The behavior of the spacer will depend on the volume and material of the holding chamber, on the electrostatic properties of the internal surface of the chamber and on the way, in which the device is used. The *in vitro* testing should be carried out by preparing the spacer and setting up the apparatus in a clinically relevant manner (which may influence the performance of the product). For example, if the manual of the manufacturer of the spacer or the holding chamber include a cleaning mode during use (weekly cleaning), it is necessary to determine the respirable fraction before and after cleaning the spacer or holding chamber. The determination of a respirable fraction can be modified to simulate the use of a spacer or a holding chamber by a patient (for example, a time respiration delay between device activation and inhalation, tidal breathing).

15. When all data collected in the development program are based on the product administered via a non-breath-operated pressurized metered dose inhaler together with one or more different spacers, the efficiency conclusion can be made only for specific, studied conditions (specific non-breath-operated pressurized metered dose inhalers and spacer(s)).

16. If the product is to be administered with and without a spacer, the use of the product alone, as well as the use of the product with a spacer must be supported by appropriate *in vitro* or *in vitro* and clinical data. If this data does not meet the criteria described in Section IV of these Guidelines, clinical data covering the relevant patients groups (e.g. children, patients treated with

inhaled glucocorticosteroids) will be required in order to investigate the impact of the spacer on efficacy and safety.

17. If there are no specific recommendations for the use of a specific spacer given in the Summary of Product Characteristics for the reference product, the test inhaled product used both with and without a spacer should be comparable with the reference product used without a spacer. If a specific spacer is named in the Summary of Product Characteristics for the reference product, the reference product should be used in accordance with the specific spacer as stated.

18. If the spacer is to be replaced subsequently by an alternative spacer, appropriate *in vitro* or *in vitro* and clinical data must be presented. It should be noted, that using the pharmacopoeial methods without taking into account clinical relevant factors, such as tidal breathing and time delays, is not acceptable. If a validated method used in comparative *in vitro* study does not show equivalence, clinical research program may be required. Clinical program must include an assessment of systemic safety through investigation of equivalence based on pharmacokinetic data or pharmacodynamic data. The highest recommended dose has to be administered, when assessing safety through pharmacodynamic equivalence.

19. The appropriately investigated spacer(s) has to be specifically named in the basic prescribing information and on the packaging.

20. If a non-breath-operated (standard) pressurized metered dose inhaler is to be used in children it must be developed for use together with a specific spacer(s) of a certain design subsequently referred to in the Summary of Product Characteristics, in the basic prescribing information (package leaflet) and also on the inhaled product packaging (hereinafter referred to as the product information). A spacer of a certain design should always be considered for use with a non-breath-operated pressurized metered dose

inhaler. When a non-breath-operated pressurized metered dose inhaler is prescribed for use in pediatric population (and not in adults), it should be provided with a spacer, that can be used with or without a face mask. The spacer has to be appropriate for the respective age groups of the pediatric population.

2. Non-pressurized metered dose inhalers

21. Non-pressurized metered dose inhalers are portable, pump activated reservoir inhalation delivery devices containing an aqueous solution, suspension or emulsion, which delivers one dose in one (or more) actuation(s) (pressing). In non-pressurized metered dose inhalers the speed of plume is decreased and, therefore, the inhalation maneuver takes longer than that for non-breath-operated pressurized metered dose inhalers (without using a spacer) and powder inhalers.

22. In order to deliver a sufficient amount of active substance, the patient has to inhale a specific volume of the aerosol. In all patients, but especially those with a limited inhalational capacity (for example, children), it has to be confirmed, that the volume required to produce the desired clinical effect does not exceed the inhalational capacity of the patient.

3. Solutions and suspensions for nebulization

23. In specific circumstances (for example, infants and young children, the severely ill patient, the elderly, the disabled), inhalation of medicinal products via a nebulizer system is a treatment option for patients with asthma and chronic obstructive pulmonary disease. Currently, jet, ultrasonic and vibrating mesh types of nebulizer systems are available and can be purchased by a patient separately from solutions and suspensions containing active substances for inhalation.

24. In a routine clinical use, inhaled products may be inhaled via any available nebulizer system, which may differ from the standard system used during the development of this medicinal product. The differences in delivered aerosol between different nebulizer systems are significant. A medicinal product formulated for inhalation via nebulizer system should be characterized for inhalation of the medicinal product using an available at the market nebulizer system and standardized nebulizer system. Representative nebulizer systems for jet, ultrasonic and vibrating mesh nebulizer systems should be studied, when establishing the characteristics of the inhalation of the medicinal product. The nebulizer system used should be described in the development program indicating:

nebulizer type;

choice of driving gas;

driving gas pressure;

driving gas flow rate;

nebulizer fill volume;

time of nebulization;

residual solute volume; and

accessories.

25. The nebulizer system(s) studied in the product development program should be described in the Summary of Product Characteristics, in the basic prescribing information (package leaflet). Warnings to be included in the product information:

that there is no information available in respect of pulmonary inhalation and deposition patterns across nebulizer systems, that have not been studied in the development program;

that the use of an alternative (untested) nebulizer system may alter the pulmonary deposition of the active substance, this, in turn, may alter the

efficacy and safety of the product, and dose adjustment may then become necessary.

If a test product has been assessed with a range of nebulizer systems, it should be clearly stated in this product information based on the results of studies, if any of these systems affect performance adversely compared with performance, when administered with other nebulizer systems.

When the product in the form of solution for nebulization has the same qualitative and quantitative composition as the reference product, the requirement for clinical studies is waived.

26. For suspensions for nebulization, therapeutic equivalence should be demonstrated through *in vivo* studies, unless justification is provided for the use of other types of studies to demonstrate equivalence.

4. Dry powder inhalers

27. Dry powder inhalers (DPIs) both using a reservoir and metering mechanism and with a pre-dispensed dose often show a high flow dependency in their deposition characteristics, when compared with non-breath-operated pressurized metered dose inhaler and non-breath-operated non-pressurized metered dose inhalers. Therefore, characterization of flow rate dependency in the patient populations, in whom the dry powder inhaler is to be used, must be presented.

28. The dossier submitted for all types of dry powder inhalers has to include sufficient *in vitro* data, including the pulmonary deposition characteristics of the product within the range of clinically relevant pressure drops/flow limits.

29. For a proposed dry powder inhaler with a high flow rate dependency (the performance of the product is highly dependent on the flow rate during use), when compared with a reference product with a low flow

rate dependency (the performance of the product is not greatly affected by the flow rate during use), then during the marketing authorization only the studied patient groups should be specified as target populations in the Summary of Product Characteristics and in the basic prescribing information in «Therapeutic Indications» Section. Extrapolation to patient populations other than those populations studied is not allowed.

30. For all dry powder inhalers, the patient population in whom the inhaler can be used (i.e. patients who can generate a sufficient minimal peak inspiratory flow to use the product) should be carefully defined.

31. The use of a high flow rate dependent dry powder inhaler as a reference product does not allow making a conclusion on the basis of the results of a clinical study on the therapeutic equivalence of the products being studied unless deposition characteristics, and inspiratory flow rates are standardized. Therefore, equivalence of these types of dry powder inhalers should be assessed across a range of inspiratory capacities (pressure drops/flow rates dependence), which represent the patient population specified in the Summary of Product Characteristics for the reference product.

5. Investigation of several product strengths

32. Dose linearity should be investigated *in vitro* for both the test and the reference inhaled products across all proposed strengths.

33. If dose linearity is demonstrated *in vitro*, when different dose strengths of a known active substance are sought, it is sufficient to establish therapeutic equivalence clinically with only one strength of this active substance. It is generally appropriate to study the lowest strength of the range available to enhance the sensitivity of the study. If linearity across all proposed product strengths is demonstrated with the test product, but not with

the reference product, the two products cannot be deemed to be therapeutically equivalent. Therefore, either the test product must be modified in such a way that it matches the reference product in terms of non-linearity (and may then be considered to be therapeutically equivalent) or therapeutic equivalence of the test product to the reference product will have to be established with more than one product strength (in the worst case, with all product strengths, depending on which product strengths of the test product are not matched in respect of linearity with the reference product).

If an additional strength of a product is to be developed, an acceptable «benefit/risk» profile for the product must be demonstrated.

The choice of reference product should be justified. The reference product should be the innovator product, if this product is available.

6. New propellants and excipients

34. When a new propellant, excipient or excipient mix is introduced the possible impact on clinical efficacy and safety must be studied in addition to any toxicological and preclinical research program. Extended safety data may be necessary. Local tolerability must be assessed and evidence of increased bronchial irritability or paradoxical bronchospasm must be sought. It may be necessary to assess any effect, that the new propellant or excipient may have on mucociliary clearance.

IV. Pharmaceutical properties of the inhaled products and the need for a clinical research program

1. New active substances

35. Products containing a new active substance are required to undergo a full development program regardless of the type of device containing a new active substance.

2. Known active substance

36. Therapeutic equivalence for generic inhaled products must be confirmed under the accelerated examination. In some cases, the use of only comparative *in vitro* data, obtained with standard methods (such as multistage impactor (impinger)), may be considered acceptable, if the product satisfies all the following criteria (compared with the reference product): the product contains the same active substance (i.e. same salt, ester, hydrate or solution, etc.);

the pharmaceutical dosage form is identical (e.g. non-breath-operated pressurized metered dose inhaler, non-breath-operated non-pressurized metered dose inhaler, dry powder inhaler, etc.);

the active substance is in the solid state (powder, suspension): any differences in crystalline structure and/or polymorphic form should not influence the dissolution characteristics, the performance of the product or the aerosol particle behavior;

any qualitative and/or quantitative differences in excipients should not influence the performance of the product (e.g. delivered dose uniformity, etc.), aerosol particle behavior (e.g. hygroscopic behavior, plume dynamic and geometry) and/or be likely to affect the inhalation behavior of the patient (e.g. particle size distribution in mouth and throat or «cold Freon» effect);

any qualitative and/or quantitative differences in excipients should not change the safety profile of the product;

the inhaled volume through the device to enable a sufficient amount of active substance into the lungs should be similar (difference within ± 15%);

method of application of the inhalation devices for the test and the reference products in order to release the required amount of the active substance should be similar;

the inhalation device should have the same resistance to airflow (difference within ± 15%);

the delivered dose should be similar (difference within ± 15%).

37. Data from the complete particle size distribution profile of individual stages of a validated multistage impactor (impinger) method should be obtained. Unless justified otherwise, comparative *in vitro* data on flow rate dependence should be obtained with a range of flow rates. This range should be justified in relation to the target patient population. The minimum (e.g. 10th percentile), median and maximum (e.g. 90th percentile) achievable flow rate in this patient population should be investigated.

38. The efficacy and safety of the medicinal product will depend on the amount of active substance, that reaches the lung and on the distribution profile. In addition, the safety will also be influenced by the rate and extent of systemic absorption from the gastrointestinal tract (i.e. the swallowed fraction). Therefore, the *in vitro* comparison should be performed for the stages, that represent the fine particle mass, as well as the upper stages of the impactor (impinger), which are relevant to the efficacy and safety of the medicinal product *in vivo*, unless otherwise justified.

39. The comparison should be performed per impactor stage or justified group of stages. At least 4 groups of stages are assessed. Justification should be based on the expected distribution levels in the lungs. At least three consecutive batches of the test product and three consecutive batches of the reference product should be tested. The maximum allowable *in vitro* difference should be indicated and justified (the standard difference acceptability level is ± 15% difference).

40. Per impactor stage or justified group of stages, the 90% confidence intervals for the observed *in vitro* differences must be calculated.

41. A conclusion regarding equivalence can only be made, if these results correspond to the maximum acceptable differences, which are indicated and justified in the pre-approved research protocol. If the product does not satisfy all of the criteria for equivalence listed in the *in vitro* protocol, *in vivo* studies should be performed to substantiate equivalence.

V. Clinical research program for inhaled products

1. Pulmonary deposition

42. Pulmonary deposition studies investigate the extent and pattern of pulmonary deposition of an inhaled active substance.

43. Excipients, devices or different aerosol characteristics of inhalation products may have a significant influence on pulmonary deposition and a significant impact on efficacy and safety. If the study product fails to show equivalence to the reference product based on *in vitro* data, one way to demonstrate equivalent efficacy may be a comparison of pulmonary deposition.

44. Pulmonary deposition studies are performed as double blind, crossover studies and should be carried out using a clinically relevant dose of the product, which may be determined from the *in vitro* data. These studies should be performed in the target patient population.

45. Pulmonary deposition can be investigated by conducting pharmacokinetic or imaging studies.

46. Although pharmacokinetic studies generate indirect data on the distribution of the product by analyzing its concentration in plasma or urine, such studies are preferable, since pharmacokinetic studies:

are easier to perform;

are safer due to the lack of radiation;

allow avoiding the risk of altering the formulation during radio-labelling; and

can demonstrate linear dose-response relationships easily.

47. Pharmacokinetic studies measure total systemic exposure (for assessment of safety), and pulmonary absorption (for assessment of pulmonary deposition and efficacy) can be separated from gastrointestinal absorption. Pharmacokinetic studies may take into account active substance released by mucociliary clearance.

48. Among limitations of pharmacokinetic studies, their inability to differentiate the distribution of drug within the different zones of the lung following inhalation should be noted. In addition, in some cases plasma/urinary concentrations are not measurable or are near the lower limit of quantification, thus, the results may be highly variable.

49. In some cases, equivalent pulmonary deposition demonstrated through pharmacokinetic studies in combination with safety data (for example, data from a systemic safety pharmacokinetic study) might be considered as sufficient demonstration of therapeutic equivalence, if justified. Therapeutic equivalence must be demonstrated through appropriate pharmacodynamic and/or clinical studies.

50. Equivalent pulmonary deposition demonstrated through imaging studies should be regarded as supportive data, when used in the assessment of therapeutic equivalence and confirmation of the equal efficacy of products.

51. If equivalent pulmonary deposition is shown through imaging studies, this should be followed by appropriate pharmacokinetic studies or appropriate clinical studies to assess therapeutic efficacy.

52. If imaging studies are used instead of pharmacokinetic studies to assess therapeutic efficacy the grounds, the studies must be fully justified.

53. In adults, pulmonary deposition studies (whenever possible) and *in vitro* characterization of the active substance, comparing the new product with a reference product, should be assessed prior to carrying out therapeutic equivalence studies.

54. In children, pulmonary deposition studies are not appropriate. Pharmacokinetic studies as a surrogate for efficacy determination only imply efficacy, they increase the burden on a child and have no sufficient advantages over pharmacodynamic and/or clinical studies in the assessment of therapeutic equivalence. Imaging studies in children are also not appropriate.

Pharmacokinetic studies

55. A pharmacokinetic study designed to assess pulmonary deposition has to be able to exclude absorption of the active substance from the gastrointestinal tract (for example, by using charcoal blockade).

56. A pharmacokinetic study may be used for determination of pulmonary deposition, but may also investigate systemic safety. In the investigation of systemic safety, total systemic exposure has to be measured in the intended patient population and, therefore, the study must include the measurement of that amount of the active substance absorbed through the lung and the gastrointestinal tract.

57. However, it may be possible for substances with negligible gastrointestinal absorption, that the pharmacokinetic study designed to assess pulmonary deposition may be sufficient in the assessment of therapeutic equivalence.

58. In accordance with the standard accepted methods of assessment of bioequivalence the maximum concentration (C_{max}), the area under the curve

(AUC) and the time to the maximum concentration (T_{max}) should be compared.

59. Equivalent pulmonary deposition and equivalent systemic safety of two inhaled products may be confirmed, if the 90% confidence interval for each parameter lies within the range of 0.8000 to 1.2500. However, in some circumstances, for example, for active substances with a narrow therapeutic window, the 90% confidence interval may require tighter limits, when assessing systemic safety. Conversely, for products with high variability, it may be acceptable to widen the acceptance range for C_{max} of 0.7500 to 1.3300.

60. If pharmacokinetic studies are carried out in children, for the assessment of systemic safety, the active substance should be measured in plasma.

Imaging studies

61. Regional quantification of the pulmonary deposition of two products can be carried out by measuring radioactivity in the different segments of the lung. Two-dimensional scintigraphic methods can be used. The whole lung percentage deposition of the drug should be measured, as well as the proportion deposited in the central, intermediate and peripheral lung zone, oropharynx, mouthpiece, actuator (trigger) and exhalation filter. Equivalent lung deposition of two drugs can be confirmed, if the 90% confidence interval of the radioactivity in each area is within a range of 0.8000 to 1.2500. It has to be assured, that the radio-labelling of the inhaled products has only negligible influence on the deposition characteristics.

2. Pharmacodynamic studies

2.1. General requirements in the investigation of therapeutic equivalence

62. Therapeutic equivalence is defined as equivalent efficacy and safety, when the new inhaled product, for which a marketing authorization is sought, is compared with an appropriate reference product. When equivalence is not shown in *in vitro* studies according to the criteria provided in subsection 2 of Section IV of these Guidelines and equivalence is not shown convincingly by investigation of pulmonary deposition and systemic safety, as provided in subsection 1 of Section V of these Guidelines, therapeutic equivalence demonstrated by means of appropriate clinical studies using well-validated study designs and comparing the test inhaled product with the reference product becomes mandatory.

63. Based on different inhalation techniques required for different inhalation devices, it is recommended, that the test and reference product should be inhaled from the same inhalation device (for example, both the test and the reference product should be administered via a non-breath-operated pressurized metered dose inhaler or both should be administered via a dry powder inhaler) wherever possible, when assessing therapeutic equivalence.

64. If clinical studies are needed and the reference product has an authorized indication, which includes both asthma and chronic obstructive pulmonary disease, therapeutic equivalence studies may only be needed in one of the patient populations. Generally, such studies are easier to carry out in patients with asthma. That is, if therapeutic equivalence to the reference product is demonstrated (in respect of both efficacy and safety) in one clinical indication (asthma), to extrapolate these results to all indications of the reference product and the use of the generic product in all patient groups, it is necessary to present an assessment of the *in vitro* studies data confirming

a comparable particle size distribution by the flow rate and the pressure drop range for the test and reference product.

2.2. Requirements for clinical studies in patients with asthma

65. Two different types of pharmacodynamic study provide acceptable methods for investigating equivalence in respect of efficacy – studies of bronchodilatation (assessment of improved airway function) and studies of bronchoprotection (study of the effect on bronchial hyperreactivity). One or other or both of these types of study may be used to satisfy the requirements of comparative efficacy. Regardless of the type of study (bronchodilatation or bronchoprotection study), the trial should be carried out in patients with asthma who demonstrate reversibility of airway function.

66. In adults, reversibility of airway function is assessed by measurement of FEV_1 with demonstration of $\geq$ 12% and $\geq$ 200 ml increase (improvement) in FEV_1 15 minutes after inhalation of an appropriate inhaled short-acting β_2 agonist (SABA);

67. In 6 years old and older children, reversibility of airway function is assessed by measurement of FEV_1 with demonstration of $\geq$ 12% improvement in FEV_1 15 minutes after inhalation of an appropriate inhaled short-acting β_2 agonist;

68. In 5 years old and younger children, spirometry is feasible in children over 3 years old, although either $FEV_{0.5}$ or $FEV_{0.75}$ may be a better measure, than FEV_1. The diagnosis of asthma is challenging in younger age group and may need to be based on clinical judgment, assessment of symptoms and physical examination data. The study carried out must be sensitive enough to be able to discriminate between the two comparator products and to be able to pick up clinically relevant differences, which might

exist between the two products. Therefore, all patients recruited to a study should be able to demonstrate a clinically relevant response to treatment.

69. Relative potency is defined as the ratio of the potency of the test product to that of the reference product and is one way of summarizing the relationship between the dose response curves of the test and reference products.

70. Demonstration of equivalence for at least two dose levels on the pharmacodynamic endpoint is another approach that can be used.

71. For either approach a minimum requirement is that the study should have a sensitivity analysis. The basis of the sensitivity analysis for the research is the need to study at least two non-zero levels and one dose level response needs to be shown to be superior to the smaller dose. It is recommended, that unless otherwise justified more than one dose of both the test and reference products are studied.

72. It is essential, that doses on the steep part of the dose response curve are studied. If a dose too low on the dose response curve is chosen, then demonstrating equivalence between two products is not convincing, as this dose could be sub-therapeutic. Equally, if a dose at the top of the dose response curve is included similar effects will be seen for doses much higher than that studied and hence demonstrating equivalence at this dose level would also not be convincing.

73. Equivalence, in respect of safety, should be demonstrated by investigation of equivalence based on pharmacokinetic data, relevant cardiovascular, biochemical and physiological parameters, and monitoring of adverse events.

74. The highest recommended dose has to be administered, when assessing safety through pharmacodynamic parameters. However, safety assessment should also be included in the efficacy studies regardless of the

dose being studied. The duration of a safety study depends on the therapeutic class of the active substance.

75. Two products will be considered as equivalent, if the following criteria are completely fulfilled:

in terms of efficacy demonstration, the comparison between products has to be performed in two ways: the first approach is to calculate the relative potency; the second approach is to compare the results of efficacy assessment for the clinical endpoint for the test and reference products at each dose studied. The results using both approaches should be provided in the efficacy assessment report. For both approaches, the observed confidence intervals comparing test and reference products should lie within the chosen equivalence margins to provide convincing evidence of equivalence. For both approaches, the chosen equivalence margins should be pre-specified and appropriately justified in the research protocol. In addition, the equivalence margins for relative potency should at least lie entirely within 0.6700 to 1.5000 range;

in terms of safety demonstration, equivalence for systemic exposure should be confirmed (if possible) by pharmacokinetic safety studies. Otherwise, equivalence in respect of relevant pharmacodynamic safety variables needs to be demonstrated. There should be no evidence, that the test inhaled product is worse than the reference inhaled product in respect of changes in vital signs, biochemical parameters and frequency of adverse events.

Bronchodilatation studies
(studies of improved airway function)

76. Equivalent therapeutic efficacy can be investigated by measurement of the bronchodilating (broncholytic) effect of the test and the reference

product through appropriate primary and secondary endpoints. The duration of the study and the choice of primary and secondary endpoints depend on the therapeutic class of the test product. In general, sensitivity of the study can be increased by the inclusion of stable, but less than optimally controlled or only partially controlled patients with asthma.

77. Less than optimally controlled asthma is defined according to pulmonary function, level of symptoms, including nocturnal symptoms and nocturnal awakening, daily activity and/or daily requirement of short-acting β_2 agonists, at baseline. The study design should include at least two dose levels. It is recommended to use (unless separately justified) a double blind, double dummy study design.

Bronchoprotection studies
(studies of the effect on bronchial hyperreactivity)

78. The bronchial hyperreactivity (bronchoprotective activity) effect of a drug against bronchial provocation can be assessed through one of the bronchoprotection studies:

with direct provocation (for example, with methacholine, histamine, acetylcholine);

with indirect provocation (for example, with adenosine monophosphate (AMP) or mannitol).

79. Bronchoprotection studies require a high degree of standardization and patient selection (for example, choice of provocation, aerosol generation, recorded nebulizer output, inhalation procedure, standardization of the physical activity of the patients eliminating diurnal variation, at least 4-fold increase in PC_{20} FEV_1 after treatment etc.). Generally, a double blind, double dummy, study design, incorporating at least two dose levels is recommended. The primary outcome variable is the provocative concentration or provocative

dose of the provocation agent, which produces a 20% fall in FEV_1 ($PC_{20}FEV_1$ or $PD_{20}FEV_1$) and must be measured at the time of the expected maximum effect of the drug.

2.3. Pharmacotherapeutic class – specific investigation of therapeutic equivalence

Bronchodilators

80. Inhaled bronchodilators are divided into three groups: short-acting β_2 adrenoceptor agonists (SABAs); long-acting β_2 adrenoceptor agonists (LABAs); anticholinergics.

81. Clinical studies of bronchodilators can have a cross-over design. An appropriate washout period between treatments has to be defined and justified in the protocol.

82. Baseline measurements prior to each treatment period have to be documented in order that any possible carry-over effects can be assessed.

Short-acting β_2 adrenoceptor agonists

83. For the short-acting β_2 adrenoceptor agonists either a single dose bronchodilatation study or a bronchial provocation study are acceptable study designs for the assessment of equivalence in respect of efficacy.

84. In adults, appropriate primary variables in the bronchodilatation model are FEV_1AUC (measurement of bronchodilatation over at least 80% of the duration of action after a single inhalation) and change in FEV_1 (at an appropriate time point(s)); in the bronchial provocation study the primary variable is either $PC_{20}FEV_1$ or $PD_{20}FEV_1$.

85. In 6 years old and older children, appropriate primary variables in the bronchodilatation model are spirometric variables: change in FEV_1, or FEV_1/FVC (forced vital capacity) ratio measured at an appropriate time

point(s), and/or FEV_1AUC measurement on bronchodilatation over at least 80% of the duration of action after a single inhalation.

86. In pre-school children, spirometry is feasible in 3 to 6 years old children, although either $FEV_{0.5}$ or $FEV_{0.75}$ may be a better measure than FEV_1, and specific airway resistance (sRaw), as measured by plethysmography or other validated methods, combined with clinical symptom scores can be used in 2 to 6 years old children. Peak expiratory flow should be measured and recorded as a secondary efficacy variable only.

87. In bronchoprotection studies, methacholine or exercise provocation can be used, for example, in 6 years old and older children. Also cold dry air challenge or eucapnic hyperventilation can be used in the pre-school child. The primary variable is either $PC_{20}FEV_1$ methacholine or $PD_{20}FEV_1$ methacholine, or percentage change from baseline in specific airway resistance (as measured by plethysmography); other validated endpoints can also be used.

88. In adults, the safety of the short-acting β_2 adrenoceptor agonists should be investigated through equivalence based on pharmacokinetic data (if it is possible, and it will be dependent on the drug and the quality of the analysis) following administration of a single dose.

89. If equivalent safety cannot be concluded from the pharmacokinetic study, safety data must be provided from a pharmacodynamic study. The safety profile must be investigated following administration of the maximum recommended dose. Recording of adverse events and assessment of any paradoxical bronchospasm, recording of vital signs and an ECG with measurement of the QTc interval, and measurement of laboratory parameters (including measurements of serum potassium and plasma glucose) will be required.

90. In children, the safety of short-acting β_2 adrenoceptor agonists should be investigated through pharmacokinetic or pharmacodynamic studies following administration of the maximum recommended dose, as stated above for adults.

Long-acting β_2 adrenoceptor agonists

91. Requirements in the assessment of equivalence in respect of efficacy of the long-acting β_2 adrenoceptors are the same as for the short-acting β_2 adrenoceptor agonists in accordance with paragraph 83 of these Guidelines. However, the onset of action (the achievement of a clinically relevant benefit), the maximum response and the longer duration of effect of the long-acting β_2 adrenoceptors must be taken into consideration in the design of the study.

92. In adults, appropriate primary variables in the bronchodilatation model are FEV_1AUC (measurement of bronchodilatation over at least 80% of the duration of action after a single inhalation) and change in FEV_1 (at an appropriate time point(s)); in the bronchoprotective provocation study the primary variable is either $PC_{20}FEV_1$ or $PD_{20}FEV_1$.

93. In children, appropriate primary variables for both bronchodilatation studies and bronchoprotection studies are as described above for short-acting β_2 adrenoceptor agonists, but with the exception of the primary variable in bronchodilatation studies in 6 years old and older children, where FEV_1AUC (measurement of bronchodilatation over at least 80% of the duration of action after a single inhalation – any shorter time period must be fully justified) is the more appropriate primary variable of choice. The dose range should be explored in single dose studies. Assessment of low and high doses to enable demonstration of dose response is required.

94. In adults, the safety of the long-acting β_2 adrenoceptor agonists should be investigated through equivalence based on pharmacokinetic data (if it is possible, and it will be dependent on the drug and the quality of the analysis) following administration of a single dose. If equivalent safety cannot be concluded from the pharmacokinetic study, safety data must be provided from a pharmacodynamic study. The safety profile must be investigated following administration of the maximum recommended dose. Recording of adverse events and assessment of any paradoxical bronchospasm, recording of vital signs and an ECG with measurement of the corrected QT (QTc) interval, and measurement of laboratory parameters (including measurements of serum potassium and plasma glucose) will be required.

95. In children, the safety of long-acting β_2 adrenoceptor agonists should be investigated through pharmacokinetic or pharmacodynamic studies following administration of the maximum recommended dose, as stated above for adults.

Anticholinergic drugs

96. The investigation of therapeutic equivalence in respect of short-acting and long-acting anticholinergic drugs is similar to that of short-acting β_2 adrenoceptor agonists and long-acting β_2 adrenoceptor agonists. However, the differing characteristics of the β_2 agonists and the anticholinergic drugs have to be taken into account particularly in respect of onset of action and duration of effect. In any bronchoprotection study the provocation agent would be a cholinergic agonist. The safety of anticholinergic drugs has to be investigated using standard approaches.

Inhaled glucocorticosteroids

97. The demonstration of equivalent efficacy of inhaled glucocorticosteroids is difficult. A successful efficacy equivalence study requires demonstration of a significant dose response relationship with the study of at least two doses of the test compared with two doses of the reference product. The doses studied should be on the steep part of the dose response curve and evidence must be provided, that the selected doses correspond to this section of the curve. In certain circumstances, the use of excessive multiple nebulizations (inhaler actuations) is needed to achieve the required dose. This may result in unacceptable impact of the product on the patient (e.g. high powder loading of the excipient from a dry powder inhaler). The use of a higher strength product only may be justified in such circumstances and comprehensive *in vitro* dose comparability for the different strength products should be demonstrated (in accordance with subsection 5 of Section III of these Guidelines).

98. Currently, the most widely used study design is the double blind, randomized, parallel group comparison of the test and the reference product. If the chosen study design differs from that specified, the reasons for this must be justified by the applicant.

99. An alternative is the double blind, randomized, crossover study, a study design, which has the potential advantage of the ability to study a smaller population. However, concerns regarding an unequal carry-over of corticosteroid effects within subjects between treatment periods and the potential difference in the baselines at the beginning of the two treatment periods must be considered. An appropriate washout period between treatments has to be defined and justified in the protocol to control the impact of any carry-over effect. The use of this type of study should be justified, including with references to previously published data of similar studies.

100. There are two different pharmacodynamic models, which can be considered in the investigation of equivalent therapeutic efficacy of inhaled glucocorticosteroids: bronchodilatation (assessment of improved airway function) model and bronchoprotection model.

101. In bronchodilatation (assessment of improved airway function) model, patients recruited should demonstrate different response to the two doses (strengths) of the inhaled corticosteroid, which are symptomatic. The population included should be clinically responsive to inhaled glucocorticosteroids and be as homogeneous a population as possible, to decrease variability and increase the power. The objective is to detect a significant dose response relationship and obtain the difference between formulations in respect of pulmonary function with a sufficiently narrow confidence interval.

In adults, the primary efficacy variable should be a pulmonary function measure and preferably FEV_1 measured regularly, if possible daily at home. Peak expiratory flow should be measured and recorded daily at home as a secondary efficacy variable. If regular measurement of FEV_1 at home is not possible, morning peak expiratory flow measured and recorded daily at home should be accepted as the main (primary) efficacy variable. Measurements of FEV_1 at least every two weeks in the clinic should always be included as a secondary efficacy variable.

In 6 years old and older children, the primary efficacy variable should also be a pulmonary function measure. FEV_1 measured and recorded daily at home, if possible, under the supervision of parents (one of parents) or a guardian is the primary variable of choice. If regular measurement of FEV_1 at home is not possible, morning peak expiratory flow measured and recorded daily at home may be accepted as the primary efficacy variable, with

measurements of FEV_1 at least every two weeks in the clinic as a secondary variable. If peak expiratory flow is not the main (primary) efficacy variable, this parameter should always be measured and recorded daily at home as a secondary efficacy variable. FEV_1 measured at least every two weeks in the clinic should always be included as a secondary efficacy variable, regardless of which primary variable (FEV_1 or peak expiratory flow) is used. The use of peak expiratory flow as a primary variable must always be justified.

In pre-school children, spirometry is feasible in 3 to 6 years old children, although either $FEV_{0.5}$ or $FEV_{0.75}$ is a better measure than FEV_1. Specific airway resistance (sRaw) measured by plethysmography or other validated methods, combined with clinical symptom scores, can be used in 2 to 6 years old children. Justification should always be provided to support the use of chosen parameters characterizing the efficacy.

The use of electronic diary cards (in both adults and children) is desirable and they should be used whenever possible. The duration of treatment period should be at least 8 to 12 weeks; any shorter treatment period should be justified. The population studied should be representative of the target product population.

102. Model of bronchoprotection is less studied alternative method, which compares inhaled glucocorticosteroids following chronic dosing.

In adults, the primary efficacy variable is the change seen in the provocative concentration or provocative dose of, for example, adenosine monophosphate (AMP), which produces a 20% fall in FEV_1 ($PC_{20}FEV_1AMP$ or $PD_{20}FEV_1AMP$). The study design should be dose sensitive and should incorporate at least two doses of the test and the reference product. Each dose

level of the test and the reference product should be inhaled for at least 4 weeks, unless otherwise justified.

In 6 years old and older children, methacholine provocation, for example, can be used to assess the change in airway hyperresponsiveness; in this case, the primary variable is the change seen in either PC_{20}FEV1 or PD_{20}FEV1. In the pre-school child, cold dry air provocation or eucapnic (in normal level of carbon dioxide in the blood) hyperventilation can be used. The primary variable is the percentage change from baseline in sRaw (as measured by plethysmography). Other validated endpoints can also be used.

The population studied should be representative of the target population, but with recruitment of patients with mild asthma and known bronchial hyperresponsiveness. The use of this type of study should be justified, including with references to previously published data of similar studies.

Whatever primary efficacy variable is chosen should be validated and be justified based on its sensitivity to detect differences between doses of the inhaled glucocorticosteroids.

103. With both models, and in both adults and children, symptom scores, percentage of symptom-free days, frequency of use of short-acting β_2 agonists and exacerbations should be recorded as secondary endpoints.

104. Other efficacy variables, which may be considered, include expired nitric oxide and sputum eosinophils, use of validated quality of life questionnaires and validated patient reported disease outcomes.

105. Equivalent safety must be demonstrated. Appropriate safety monitoring within the therapeutic efficacy studies should include the

recording of local adverse effects and any evidence of paradoxical bronchospasm and the assessment of systemic effects.

106. Systemic safety should be demonstrated through pharmacokinetic equivalence in adults (if it is possible, and it will be dependent on the drug profile and the quality of the analysis). If safety cannot be assessed in this way, assessment of systemic safety following inhalation of the maximum recommended total daily dose of the inhaled glucocorticosteroids, together with the assessment of a lower dose administration, regularly over time, through measurement of pharmacodynamic parameters related to pharmacokinetic parameters will be required.

107. In respect of the pharmacodynamic assessment of systemic effects of ICSs in adults, it is necessary to assess the effect on the hypothalamic pituitary adrenocortical (HPA) axis. The preferred pharmacodynamic method of assessing the hypothalamic pituitary adrenocortical axis is the repeated assessment of the change from baseline in 24-hour plasma cortisol, as measured by AUC (as the primary variable) and C_{max}. The duration of treatment in such a study must be justified and must ensure, that steady state has been reached in order that the potential systemic effects of the inhaled glucocorticosteroids, both the test and the reference, can be assessed and compared. The study should be carried out in patients with asthma. All measurements should be carried out in a controlled and fully tested environment. To achieve this, patients should be at in-patient clinic on those days, when assessments are being carried out.

108. In children, safety data cannot be extrapolated from data generated in adults with asthma or from a surrogate adult population. The cases, when evaluation of safety in children is necessary, are described in Section VIII of these Guidelines.

109. Systemic safety should be demonstrated through pharmacodynamic equivalence using two different, but relevant tests or through pharmacokinetic equivalence, if it is possible and justifiable.

110. The use of pharmacokinetic data will be dependent on the drug and the quality of the analysis and should be considered only if there is sufficient published information on the systemic effects of the reference product on the hypothalamic pituitary adrenocortical axis in children. If the use of pharmacokinetic data is fully justified, it may be sufficient in the assessment of equivalent systemic safety in children. Therefore, systemic safety in children should be demonstrated by fulfilment of at least one of the following conditions:

two pharmacodynamic tests of safety – an assessment of the systemic effects of inhaled glucocorticosteroids on the hypothalamic pituitary adrenocortical axis and an assessment of growth (using a surrogate marker), or

a pharmacokinetic assessment, if it is possible and justifiable.

111. The current view, in respect of the pharmacodynamic assessment of systemic effects of inhaled glucocorticosteroids in children, is to assess the effect on the hypothalamic pituitary adrenocortical axis and on lower leg bone growth rate (knemometry) as a surrogate marker for growth.

112. In children, the following tests of hypothalamic pituitary adrenocortical axis function may be considered:

repeated assessment of the change from baseline in 24-hour plasma cortisol, as measured by AUC (as the primary variable) and C_{max}. The duration of treatment in such a study must be justified and must ensure, that steady state has been reached in order that the potential systemic effects of the inhaled glucocorticosteroids, both the test and the reference, can be assessed and compared. The study should be carried out in a population of

children with asthma and, if possible, all measurements should be carried out in a controlled environment. To achieve this, children should be at in-patient clinic on those days, when assessments are being carried out;

the 24-hour urinary-free cortisol is a variable, which could be used in the assessment of systemic effects of inhaled glucocorticosteroids on the hypothalamic pituitary adrenocortical axis, although this test is appropriate for the assessment of high urinary levels of cortisol. Difficulties are always encountered in the collection of urine samples, which are often incomplete, thus, the data is very difficult to interpret and subsequently may be of little value. Therefore, such a test of hypothalamic pituitary adrenocortical axis function is not considered to be the most appropriate test, but, if used, urine should be collected in a controlled environment. To achieve this, children should be at in-patient clinic on those days, when urine collections are being made.

Assessment of the hypothalamic pituitary adrenocortical axis using spontaneous cortisol secretion may identify only those children with fairly profound abnormalities of the hypothalamic pituitary adrenocortical axis, that are evident in the unstressed state. Most commonly, children treated with inhaled glucocorticosteroids have normal cortisol profiles in the unstressed state, but cannot respond with an appropriate increase in serum cortisol during times of stress (i.e. infection, trauma, etc.). These children may not be identified by measurement of either plasma or urinary cortisols, as described above. Therefore, it is important, that the assessment of systemic safety in children should always include two different pharmacodynamic tests of safety described above and whichever tests are chosen should be justified.

113. Growth rate should not be considered as the most appropriate single measure of the systemic effects of inhaled glucocorticosteroids, growth in a child may be normal, but the hypothalamic pituitary adrenocortical axis

may be suppressed. At the same time, the assessment of growth should be considered alongside the assessment of effects on the hypothalamic pituitary adrenocortical axis, when systemic safety is demonstrated through pharmacodynamic equivalence studies with the following:

accurate measurement of linear growth for 12 months or longer (preferred method) and body weight evaluation;

knemometry, which is not a measure of linear growth, but a sensitive pharmacodynamic measure of systemic steroid exposure demonstrating an effect of inhaled glucocorticosteroids on slowing the lower leg bone growth rate. Short-term changes seen in the slowing of the lower leg bone growth rate over 4-8 weeks, as measured by knemometry appear to correlate poorly with linear growth measurements and may lead to an overestimation of any potential effects of glucocorticosteroids on person's growth. However, knemometry is a sensitive and useful technique as a surrogate marker of growth, if the test product is being compared with a well-known reference product with a well-defined safety profile. Knemometry used in this way could be an indicator of equivalence. Knemometry is validated, accurate and reproducible, but long-lasting, and, therefore, the duration of study, if less than 4 weeks, should be justified.

114. If pharmacokinetic studies are carried out in children for the assessment of systemic safety, the active substance should be measured in plasma.

115. Whatever methods of assessing systemic effects of inhaled glucocorticosteroids are used in either adults or children, they should be discussed fully and justified in the research program and in the registration dossier.

116. According to paragraph 26 of the Rules for Registration and Expert Examination of Medicinal Products for Medical Use approved by the

Decision of the Council of the Eurasian Economic Commission of November 3, 2016 No. 78, the originator (manufacturer) may to apply to the authorized bodies or expert organizations of the Member States for scientific and pre-registration consultations in accordance with the legislation of the Member States.

2.4. Product type-specific investigation of therapeutic equivalence

Combination products

117. For fixed combination products of known active substances, where the combination of specific active substances is not new and for which there are reference combination products, therapeutic equivalence should be demonstrated for each of the active substances of a fixed-dose combination product and study design will depend on the specific active substances in the combination. For example, efficacy and safety of the combination of an inhaled glucocorticosteroids and a long-acting β_2 adrenoceptor agonists might be investigated in one study, in which assessment criteria capable of assessing both active components in the combination separately are provided (co-primary variables in respect of efficacy will need to be defined, one for each component of the combination). The study design should include two doses of each combination product (the test and the reference combination product) in order to show a significant statistical dose response relationship.

118. In addition to establishing therapeutic equivalence for combinations of inhaled glucocorticosteroids with long-acting β_2 adrenoceptor agonists, separate studies assessing each separate active component can be conducted. The efficacy of the long-acting β_2 adrenoceptor agonists' component can be assessed following inhalation of a single dose through either measurement of bronchodilatation over at least 80% of the

duration of its action or bronchial airway studies; the efficacy of the inhaled glucocorticosteroids component will be through the study of multiple dose inhalations over time.

119. For new combination products (fixed combination products) with no approved fixed combination reference product the inclusion of treatment arm, in which patients would receive the inhaled glucocorticosteroids component alone in addition to the treatment group using a combination is necessary. The inhaled glucocorticosteroids alone treatment group could receive the same dose of corticosteroid as in the combination product or alternatively it is acceptable to receive a higher dose. Subsequent registration of such products will require a complete research program in the dossier.

120. The assessment of the safety of combination products is the same as for the single active substances, and it is described above in subsection 2 of Section V of these Guidelines.

121. In children, the development of combination products should be as described above in subsection 2 of Section V of these Guidelines unless otherwise justified.

Inhalation packs and special means in inhalation therapy

122. Inhalation packs are only acceptable in very exceptional circumstances, taking into account the required justifications. Such cases can be classified as:

improvement of the benefit/risk assessment due to addition or potentiation of therapeutic action of the active substances compared with the single active substance;

improved patient compliance and adherence to therapy, when compared with the same therapy administered as separate active substances, administered via separate devices, provided, that this combination of active

substances is already known and recommended in combination therapy. The clinical relevance of this improved patient compliance and adherence to therapy has to be obtained from adequately designed studies in the target patient population.

123. According to paragraph 26 of the Rules for Registration and Expert Examination of Medicinal Products for Medical Use approved by the Decision of the Council of the Eurasian Economic Commission of November 3, 2016 No. 78, the originator (manufacturer) may to apply to the authorized bodies or expert organizations of the Member States for scientific and pre-registration consultations in accordance with the legislation of the Member States on the question of the form for filing an application for the registration of an inhaled product in the form of a combination pack.

VI. Clinical trials and change of pharmaceutical specifications

124. Product specifications should be set based on pharmaceutical data from the product batches used in the clinical studies. Any changes to these specifications (for example, fine particle dose) should also be based on data from these clinical batches.

125. A widening of the of clinically substantiated limits of test results on the quality indicators included in the specification cannot be carried out after the completion of clinical studies without reviewing the conclusions of the clinical program.

VII. Products for the treatment of chronic obstructive pulmonary disease

126. Clinical studies of this group of products should be carried out in accordance with the requirements of subsection 2 of Section V of these Guidelines. Therewith, it is not allowed to use the indicators established for

the population of patients with asthma as the study objectives. The indicators used in the clinical study of drugs for the continuous (supporting) therapy of patients with chronic obstructive pulmonary disease should be established as the study objectives.

VII. Special aspects of the study of inhaled products in children and adolescents

127. In the development of inhaled products for use in children and adolescents, where therapeutic equivalence between two inhaled products must be demonstrated, pharmacokinetic and pharmacodynamic and/or clinical studies will be required. Such studies may be required across the entire age range of childhood, and may need to be performed separately for each of the following sub-groups: less than 2 years old, 2-5 years old and 6-12 years old.

128. The clinical development may also include studies in adolescents. Justification will be required for which age groups are studied and which are not.

129. Data generated in adult populations should be considered in the development of the product in children. However, there is a number of differences between adults and children and particularly younger children (and between children with asthma and children with normal airway function), which might influence product efficacy and safety in children. Therefore, extrapolation from studies in adults, or from studies in adults coupled with *in vitro* data, or the study of a surrogate adult population or the study of normal healthy children may be unsafe and unjustified. Products may be equivalent in adults, but may not be equivalent in children.

130. The airway in younger children differs from the airway in adults. This leads to the fact, that the amount of the dose of an inhaled drug reaching

the lower airway in a younger child will differ from the delivered amount of a drug in an adult. A child shows different breathing patterns and has differing tidal volumes, airway geometry, etc. compared to adults. Resistance and inspiratory flow differ between an older child and a younger child.

131. Characteristics of the delivery device can make it unfit for correct use of a child. This may result in a changed risk/benefit relationship in a child compared with that seen in an adult due to the following:

a non-breath-operated pressurized metered dose inhaler used by a younger child does not allow to achieve the same effect as in adults, since younger children are unable to provide the necessary level of coordination of the inhalation of the drug and the launch of the device, which, as a result, can lead to a loss of therapeutic effect;

use of a spacer together with a non-breath-operated pressurized metered dose inhaler may increase the amount of the inhaled dose of the drug deposited in the lung by up to 200% depending on the characteristics of the spacer and the child’s age and inhaler technique. When comparing two products administered via non-breath-operated pressurized metered dose inhalers, equivalence may be demonstrated, that may not be observed, when used with a spacer;

the internal resistance of the dry powder inhaler may be such that a child will find the inhaler more difficult to use, than an adult would. Therefore, when comparing two dry powder inhalers, which may be equivalent in adults, equivalence may not be demonstrated in children characterized by a lower peak inspiratory rate (peak inspiratory flow).

132. Risks of use and adverse effects of inhaled glucocorticosteroids differ across different age groups. Children and young adults are more susceptible to the systemic adverse effects, including the life-threatening effects of inhaled glucocorticosteroids, than older adults. Therefore, when

products showed to be equivalent in adults with regard to systemic safety, this may not be applicable as evidence of equivalent safety in children. Conversely, local adverse effects are much less common in children, than in adults. Thus, differences between the test and the reference product may be clinically irrelevant in adults, but clinically relevant in children.

133. Therefore, if the new product is to be used in children, confirmation of both equivalent effectiveness and equivalent safety in this children's age group is required. The dose range for use in children must be defined. The lowest limit of the dose range for the reference product as authorized for use in children must be achievable with the new product (both with a specific appropriate spacer and without a specific appropriate spacer, if the active substance is delivered via a non-breath-operated pressurized metered dose inhaler); sometimes the development of a new lower dose will be required. If the reference product is not authorized for use in children, full clinical development of the new product in children, which must include determination of the dose range, the dosing interval, the minimally effective dose and the maximum total daily dose, will be required. In addition to the demonstration of equivalent efficacy, assurance must be provided that the safety profile is unchanged or improved compared with that of the reference medicinal product, particularly in respect of systemic safety at the top of the proposed dose range.

134. If children population is included in the indications for the use of the medicinal product, the following algorithm for the clinical development of the drug should be used:

a) clinical studies in children will not be required, if all the criteria for equivalence have been fulfilled in the *in vitro* equivalence study in accordance with subsection 2 of Section V of these Guidelines, and one of the following conditions is fulfilled:

the inhalation device of the test product intended to use in children is identical to the inhalation device of the reference product;

the pharmaceutical dosage form of the test product is a non-breath-operated pressurized metered dose inhaler with the same spacer as recommended for use with the reference product, which is used in the intended pediatric population or the dosing device of the test product is provided with a spacer, similarity of which has been verified in accordance with subsection 1 of Section III of these Guidelines;

b) waiver of clinical studies in children may be justified, if all the criteria for equivalence have been fulfilled in the *in vitro* equivalence study in accordance with subsection 2 of Section V of these Guidelines and all of the following conditions are fulfilled:

the inhalation device of the test product is not identical to the inhalation device of the reference product;

the inhalation device of the test product is approved in the intended pediatric population with a product containing another active substance.

To justify a waiver of clinical studies in children, comparative *in vitro* data between the test and the reference product demonstrating comparable particle size distribution in view of the flow rate, pressure drop range and air volume clinically applicable to children should be presented (in accordance with the requirements of subsection 4 of Section IV and subsection 2 of Section V of these Guidelines). However, if there are differences in flow rate between the test and reference products, therapeutic equivalence of such products in children has to be demonstrated through appropriate studies;

c) as a minimum, clinical study in the pediatric population will be required to ensure, that a child is able to perform the minimal breathing trial (generate minimal peak inspiratory flow necessary to trigger the inhalation device), if all the criteria for equivalence have been fulfilled in the *in vitro*

equivalence study (in accordance with subsection 2 of Section V of these Guidelines) and all of the following conditions are fulfilled:

the inhalation device of the test product is not identical to the inhalation device of the reference product, which is used in the pediatric population;

the inhalation device of the test product is used in adults, but it is not approved in the pediatric population (the device had never been used in children).

The results of such a clinical study of child's ability to perform the minimal breathing trial must be accompanied by the results of *in vitro* comparative study between the examined and the reference inhaled products demonstrating comparable particle size distribution in view of the flow rate, pressure drop range and air volume clinically applicable to children should be presented. However, if there are differences in flow rate between the test and reference inhaled products, therapeutic equivalence of such products in children has to be demonstrated through appropriate studies.

135. If none of the above apply, clinical development of the product in children, including demonstration of therapeutic equivalence in respect of both efficacy and safety, will be required. Equivalent efficacy must be demonstrated through appropriate pharmacodynamic and/or clinical efficacy studies (or bronchodilatation studies, which assess airway function improvement, or bronchoprotection studies). Clinically validated and age-relevant efficacy variables (both primary and secondary, as necessary) must be evaluated. The evidence base to date in respect of the best (preferred) methods to use in the assessment of either bronchodilatation or bronchoprotection in children is limited, and, therefore, assessment should be based on an individual approach, taking into account the current research findings and the views of experts in the field. Justification should be provided to support the chosen parameters characterizing the efficacy.

136. Equivalent safety must also be demonstrated. Systemic safety should be demonstrated through pharmacokinetic equivalence study results, if it is possible and justifiable, or through pharmacodynamic equivalence. The possibility of use of pharmacokinetic data will be dependent on the drug and the quality of analysis. If the use of pharmacokinetic data is justified, pharmacokinetic data alone may be sufficient for the admission of equivalent systemic safety in children. For pharmacodynamic assessment, assessment of the maximum recommended total daily dose regimen, together with the assessment of a lower dose regimen, over an appropriate time period, will be required.

137. It is essential to provide data, demonstrating that the study has sufficient sensitivity and the ability to confirm, that the test and the reference inhaled products are therapeutically equivalent.

138. If different age groups of children are included within a single clinical study, stratification by age group should be carried out.

139. In addition to the above provisions, with regard to the pharmaceutical development of inhaled products for the treatment of asthma in children, the provisions of subsections 1 and 2 of Section V of these Guidelines should be followed to confirm their therapeutic equivalence. However, if therapeutic equivalence is confirmed by the analysis of the clinical efficacy endpoints, the equivalence margins should be specifically justified, and not simply extrapolated from those used in adults. The justification of the chosen equivalence margins should take into account the age of the subjects and the severity of their asthma.

Special aspects of the clinical studies in adolescents

140. For 12 to 17 years old adolescents population, admission of the therapeutic equivalence based on the data generated in studies in adults may

be possible, if specific studies have been carried out in less than 12 years old children. If a separate study is not possible, a sufficient number of adolescents should be recruited to adult studies, so that the entire intended age range (12 years old to the elderly age) has been studied. Stratification in 12 to 17 years old and 18 years old and older age groups is not necessarily required. However, data generated (as both efficacy and safety data) from the two age groups should be documented and analyzed separately, if possible. If studies have not been carried out in children (less than 12 years old), the generation of clinical data in the adolescent as part of a separate study may be required.

VIII. Clinical studies of inhaled products for confirmation of safety of new excipients

141. Since the safety profile of currently used known excipients is well characterized, including that in the composition of inhaled products, additional safety studies for such drugs are not required. Where new excipients are used in inhalation products, safety of which has not been investigated in humans previously, potential problems associated with both the safety of such excipients and their possible interactions with active drug substances, which might enhance the drug’s toxicity. A change in excipients might result in changes in drug deposition patterns within the lung, which might affect absorption and systemic safety. Full animal toxicology study will have been carried out for each new excipient, but such data does not exclude the need for clinical safety studies in human.

142. The safety study program in this situation has two objectives:

to determine the safety of a new excipient in the composition of a medicinal product;

to assess interactions, which may occur between an active drug substance and a new excipient, or a new excipient combination, which might result in changes in the safety of the medicinal product.

143. The assessment of a new excipient or a new excipient combination will be required only once, but the assessment of interactions will be required for each active substance combined with that new excipient or new excipient combination. Obviously, if changes in systemic safety or absorption are seen in these interaction studies, these changes will require a quantitative assessment and a long-term safety assessment.

144. A change in excipient or the excipient combination will require further long-term safety assessment.