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TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

GUIDANCE ON THE QUALITY AND CLINICAL REQUIREMENTS FOR INHALATION AND NASAL MEDICINAL PRODUCTS

(Made under Regulation 4 (1) of the Tanzania Medicines and Medical Devices (Registration of Medicinal Products) Regulations, 2015

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TMDA Headquarters, Plot No. 56/1, Block E, Kisasa B Centre, Hombolo Road, P. O. Box 1253, Dodoma - Tanzania,
Tel: +255 (26) 2961989/2061990/ +255(22) 2450512/2450751/2452108,
Email: info@tmda.go.tz, Toll free: 08001100834

TABLE OF CONTENT

ABBREVIATION OF TERMS

API	-	Active Pharmaceutical Ingredient
APSD	-	Aerodynamic Particle Size Distribution Breath Operated Inhaler
AUC	-	Area under the plasma concentration curve
BOI	-	Breath Operated Inhaler
BP	-	British Pharmacopeia
C_{max}	-	Maximum or peak plasma concentration
DD	-	Delivered Dose
DPI	-	Dry Powder Inhaler
EMA	-	European Medicines Agency
FPD	-	Fine Particle Dose
FPM	-	Fine Particle Mass
GSD	-	Geometric Standard Deviation
MMAD	-	Mass Median Aerodynamic Diameter
OIP	-	Orally Inhaled Products
PD	-	Pharmacodynamic
PK	-	Pharmacokinetic
pMDI	-	Pressurized Metered Dose Inhaler
T_{max}	-	Time to Cmax
TMDA		Tanzania Medicines and Medical Devices Authority
UDD	-	Uniformity of Delivered Dose
USP	-	United States Pharmacopeia
WHO	-	World Health Organization

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Dr. Yonah H. Mwalwisi
DIRECTOR OF HUMAN AND VETERINARY MEDICINES

GLOSSARY OF TERMS

For the purpose of this guidance the following terminologies are applicable.

Comparator product

Means a pharmaceutical product with which the generic product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety and quality have been established.

Delivery device

Means the sum of component(s) of the container closure system responsible for delivering the drug to the respiratory tract (inhalation product) or the nasal and/or pharyngeal region (nasal product).

Extractables

Means the compounds which may be extracted from the container closure system by using stressful conditions.

Fine particle dose (FPD) or Fine Particle Mass (FPM)

Means the same amount of particles ≤ 5µm per actuation/puff or dose that are delivered to the lung.

Generic product

Means a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

Inhalation medicine

Means a drug product (including the delivery device, where applicable) whose intended site of deposition is the respiratory tract. The site of action may be local or systemic.

Leachable

Means the compounds which may leach from the container closure system into the formulation under normal conditions of storage and use.

Spacer

Means a spacing device and is also known as a valved holding chamber. It aids inhalation.

Strength/dose

Means an amount of drug that is metered in the device for a single inhalation manoeuvre whereas a single dose may contain for example 2 puffs of a pMDI or 4 puffs of a pMDI. So, for example, for doses of 12µg and 24µg formoterol pMDI one and 2 puffs of the 12µg strength or two puffs of both the 6µg and 12µg strength might be used.

Pulmonary deposition

Means an amount of active substance deposited in the airways (mouth and throat excluded).

FOREWORD

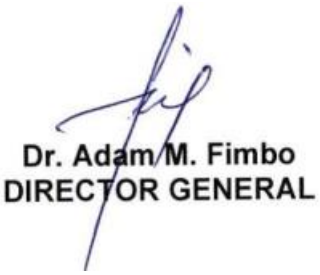
This is the first edition of the guidance on the quality and clinical data requirements for inhalation and nasal products. The guidance also provides specific requirements for variations to existing medicines. The document aims to guide applicants on the quality and clinical data requirements that should be submitted to support marketing authorization of nasal spray and inhalation medicinal products.

The use of inhaled drug products, such as metered dose inhalers (MDIs) and nasal dry powder inhalers (DPIs), is becoming increasingly common despite the known challenge of ensuring uniform dose delivery. The effectiveness of these products depends not only on the formulation but also on the delivery device and the patients' experience, including coordination skills during their use.

Due to the complexity in their delivery, predicting clinical outcomes has been challenging. The published TMDA's Compendium Guidelines for Marketing Authorization of Medicinal Products does not fully address the specific issues relating to these products.

This document addresses specific issues relevant to medicinal products and delivery devices but may not be able to offer complete guidance on every aspect of the quality and clinical documentation for the product. Therefore, this guidance should be read in conjunction with other relevant guidelines cited in this guidance.

It is anticipated that this document will provide guidance to applicants to prepare and compile complete documents to support their applications for marketing authorization. This will facilitate efficient review and avoid queries that result in unnecessary delays in the approval of the medicines, thus improving access to quality, safe, and efficacious assured medicines for patients.



Dr. Adam M. Fimbo
DIRECTOR GENERAL

1. INTRODUCTION

1.1 Background

Nasal spray and inhalation products are used to treat respiratory infections and lung diseases characterized by airflow obstruction and shortness of breath, including asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis.

These dosage forms have unique characteristics as their performance is dependent not only on the active pharmaceutical ingredient and excipients but also on the container closure system, including delivery devices such as the valve and metered system. The products are designed to deliver the active ingredients to the nasal mucosa, pharyngeal region, and lungs.

The intended site of action of the active ingredient can be local or systemic:

i. Inhalation medicines are intended to be deposited in the respiratory tract.
ii. Nasal spray medicines are intended to be deposited in the nasal or pharyngeal region.

Inhalation and nasal spray medicines typically exhibit more variable bioavailability compared to medicines administered through other routes due to the variability in usage, such as the patient's inspiratory flow pattern.

This document provides guidance to applicants on the quality and clinical data requirements that should be submitted to support the marketing authorization of nasal spray and inhalation medicinal products, including variations to existing medicines. It covers both single active pharmaceutical ingredient products and combination products.

Furthermore, this guidance addresses specific issues related to the performance of delivery devices. Given the wide diversity of inhalation and nasal products in terms of delivery devices, applicants are expected to refer to other relevant references, such as the United States Pharmacopeia, European Pharmacopoeia, and ISO standards.

1.2 Scope

The scope of this guidance encompasses products that are intended to administer the active pharmaceutical ingredient to the lungs, nasal mucosa, and pharyngeal region. This includes various delivery systems such as pressurized metered dose inhalers, dry powder inhalers, nebulization products, non-pressurized metered dose inhalers, pressurized metered dose nasal sprays, and nasal powders.

It's important to note that this guidance does not apply to systemically acting medicines, liquid inhalation anaesthetics, nasal ointments, creams, and gels. These types of products are not within the scope of this particular guidance document.

2. QUALITY

2.1 Quality guidelines

Specific guidelines that should be referred to for the quality requirements of inhalation and nasal products include:

i. Guideline on the pharmaceutical quality of inhalation and nasal products (EMEA/CHMP/QWP/49313/2005 Corr);

ii. WHO Guideline on stability testing of active pharmaceutical ingredients and finished pharmaceutical products (WHO Technical Report Series, No. 1010, Annex 10, 2018);

iii. Guideline on process validation for finished products – information and data to be provided in regulatory submission (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1).

In addition to the above guidelines, applicants are advised to refer to the following pharmacopeia general monograph and chapters:

i. The BP general monograph for Preparations for Inhalation;

ii. USP general monograph <5> Inhalation and nasal drug products—general information and product quality tests;

iii. USP chapter <610> Inhalation and Nasal Drug Products: Aerosols, sprays, and Powders – Performance Quality Tests;

Note: the current version of the referenced documents should be used during the application process, and any changes to the reference documents should also be applied to applications for registration submitted to TMDA.

2.2 Delivery devices

The development of the delivery device should be thoroughly described. Any changes made in the design, such as modifications to component materials, or manufacturing process, such as scaling up from single cavity to multiple cavity tooling, during the product development should be discussed in terms of their impact on the performance characteristics of the product. This includes parameters (e.g., delivered dose, fine particle mass, etc.).

To demonstrate the equivalence of the comparator product with the product intended for marketing, appropriate comparative data on the generic product should be provided.

For device-metered dry powder inhalers, measures should be in place to prevent unintentional multiple dose metering and subsequent inhalation by the patient. Data should be provided to demonstrate that all target patient groups are capable of triggering the delivery device in breath-activated devices. This can be evaluated as part of the clinical program during patient handling studies. The triggering mechanism should be well-characterized as part of the delivery device development program.

For device-metered dry powder inhalers, each unit should have a counter or other fill indicator to provide the patient with an indication of when the number of actuations stated on the label has been delivered. Including dose counters is also encouraged for other multiple dose products.

2.2.1 Rubber or plastic in delivery devices

The following additional information should be provided: -

i. Identify each material, the formulation code and the manufacturer
ii. Include evidence of the biological safety of all components
iii. Provide test certificates or reports to demonstrate compliance if the evidence refers to a monograph in a recognized pharmacopoeia
iv. Include details of any extractable or leachable studies performed if your product contains a liquid or gas, because substances can leach from rubber or plastic material in valve components or gaskets of delivery devices (in Module 3.2.P.2.4). For more information, go to EMEA/CHMP/QWP/49313/2005 Corr Section 4.2.1.3.

This information should be provided in section 3.2.P.2.4 (selection of container closure) and 3.2.P.7 (container closure system).

2.2.2 Colour of delivery devices

If the colour of the delivery device is not similar to that of the comparator product:

i. Provide a clinical justification for the colours used
ii. Discuss safety issues around how a user will recognise the difference between different medicines.

2.2.3 Counters

Counters and fill indicators let the user know when they need to replace the inhaler.

i. If the comparator product has a counter or fill indicator, then a generic product needs to have one too

ii. If the comparator product does not have a counter or fill indicator, then the generic product does not need to have one, although it is recommended to include a counter or fill indicator for all multiple dose inhalation medicines.

3. REQUIREMENTS FOR DEMONSTRATION OF THERAPEUTIC EQUIVALENCE

This section outlines the requirements for designing, conducting, and evaluating the therapeutic equivalence of inhalation and nasal products. The data provided should demonstrate the equivalence between the comparator product and the generic product, aiming to establish the safety and efficacy of the product intended for marketing authorization.

For generic products to be considered acceptable, they must be of satisfactory quality and therapeutically equivalent to the comparator product in terms of the following aspects:

i. Dosage forms;
ii. Strengths; and
iii. Indications and directions for use.

3.1 Choice of the comparator product

For in-vitro, pharmacokinetic and clinical efficacy studies of inhalation products and nasal medicines, the acceptable comparator product should be used.

General principles for the selection of comparator products are described in the Annex IV of Compendium of Guidelines for Marketing Authorization of Human Medicinal Products, 1st revision, July, 2020: *Selection of a comparator product to be used in establishing interchangeability*.

3.2 Therapeutic equivalence guidelines

Due to the complexity of the formulation and method of administration, specific studies are necessary to demonstrate the therapeutic equivalence between the comparator product and the generic formulation of inhalation and nasal products. To establish this equivalence, the following specific guidelines should be consulted:

i. Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents (CPMP/EWP/4151/00 Rev 1);

ii. Note for guidance on the clinical requirements for locally applied, locally acting products containing know constituents (CPMP/EWP/239/95); and

iii. Questions and Answers: positions on specific questions addressed to the Pharmacokinetics Working Party (EMA/618604/2008 Rev. 13): Question 17 Evaluation of orally inhaled medicinal products.

The above guidelines are not exhaustive, therefore other recognized publication or other relevant references may be used. Furthermore, any changes to the reference documents shall also apply to applications for registration submitted to TMDA.

3.3 Specific requirements

3.3.1 Metered-dose nasal sprays, solutions

Demonstrate similarity between the proposed product and the comparator products by the following parameters:

i. Qualitative and quantitative formulation, as described for inhalation medicine solutions;
ii. Droplet size distribution, including data to show the fraction of droplets under 10 µm is very small;
   - Do not use an impactor that only measures droplets smaller than 12 µm, because most of the droplets will be larger than 12 µm;
iii. Delivered dose and delivered volume; and
iv. Spray times, spray pattern and plume geometry.

These should be generated using validated methods.

Droplet size for local effects

When the medicine is intended to have local effects, the droplets for nasal spray medicines should generally be larger than 10 µm. This prevents unwanted deposition in the lower airways.

It should be demonstrated that, the droplet size distribution of the aerosol cloud is appropriate for nasal administration and the number of droplets below 10 µm is low and controlled. In addition, smaller droplets deposit in the nasal cavity may be demonstrated, depending on the velocity and direction of the aerosol cloud.

Droplet size for systemic absorption

When the medicine is intended for systemic absorption, the optimal droplet size is about 5 µm for nasal spray solutions or suspensions. This gives good distribution in the nasal area and slow clearance.

3.3.2 Metered-dose nasal sprays, suspensions

All prescribed requirements under metered-dose nasal spray solutions are applicable for metered-dose nasal sprays, suspensions. Additionally, it is necessary to establish that both the proposed and comparator products have the same solid state properties as follows: -

i. Particle size distributions of the suspended active pharmaceutical ingredient within the droplets - if any of the excipients are also in suspension, the test method need to be able to distinguish between particles of the active pharmaceutical ingredient and particles of excipients; and

ii. Morphology of the particles of active pharmaceutical ingredient within the droplets

Several methods can be used to determine the particle size distribution and morphology, including:

a) laser diffraction;
b) optical microscopy (with or without a polarising filter or a dye, which can often distinguish between active pharmaceutical ingredient and carrier);
c) Raman microscopy; and
d) scanning electron microscopy, with or without energy-dispersive X-ray spectroscopy (EDS), which can often distinguish between active pharmaceutical ingredient and carrier.

3.3.3 Solutions for nebulisation

Physicochemical properties of solution for nebulization i.e., pH, buffer capacity, density, surface tension, viscosity and osmolality a significant impact on the deposition and absorption characteristics of the product. These properties can ultimately affect the safety and efficacy of the medication. Therefore, it is crucial to conduct a detailed analysis to ensure that the physicochemical properties of the proposed formulation are similar to those of the comparator product formulation. To assess the physicochemical properties, a validated analytical method should be employed.

When the generic product is an aqueous solution for nebulization, intended to be administered with essentially the same device, contain the same API(s) in the same

concentration and contain the same excipients in similar concentrations as the comparator product the requirement for *in vitro and/or in vivo* therapeutic equivalence studies may be waived.

3.3.4 Suspensions for nebulisation

For suspensions intended for nebulization, it is necessary to provide data demonstrating the similarity between the proposed product and the comparator product in the following aspects:

i. Qualitative and quantitative formulation: the formulation contains the same API(s) in the same concentration and contain the same excipients in similar concentrations as the comparator;
ii. Particle morphology of the active pharmaceutical ingredient in the suspension;
iii. Particle size distribution of the active pharmaceutical ingredient in the suspension: the test method needs to be able to distinguish between particles of the active pharmaceutical ingredient and particles of excipients if any of the excipients are also in suspension; and
iv. Droplet size distribution of the nebulised droplets: use appropriate methods to test droplet size.

3.3.5 Metered-dose inhalation medicinal products

For metered-dose inhalation medicinal products, the therapeutic equivalence should be demonstrated in a stepwise approach. These major steps include *in vitro* equivalence studies (step 1), pharmacokinetic studies (step 2) and pharmacodynamic studies/ clinical studies (step 3). Therapeutic equivalence is established if the requirements of one “step” are fully met.

3.3.5.1 *Step 1: In vitro Studies*

For generic products, therapeutic equivalence can be established based on the fulfillment of the *in vitro* studies acceptance criteria established in the guidelines (CPMP/EWP/4151/00 Rev 1).

In vitro studies might be sufficient for generic product containing known active pharmaceutical ingredient criteria. The following criteria are applicable for establishing equivalence with respect to in vitro studies data:

i. The drug product contains the same active pharmaceutical ingredient as the reference product in terms of the salt, ester, hydrate, solvate etc.;
ii. The pharmaceutical dosage form is identical;

iii. In case where the active pharmaceutical ingredient is in the solid state, i.e., as a powder or suspension, different crystalline structures and/ or different polymorphic forms should do not affect the product performance;
iv. Qualitative and/ or quantitative differences in composition have no impact on the drug product performance or inhalation behavior of the patient;
v. Qualitative and/ or quantitative differences in composition do not affect the drug safety;
vi. The inhaled volume through the device is similar, i.e., 15 % deviation is allowed;
vii. The handling of the device is similar compared to the reference drug product;
viii. The device resistance is similar, i.e., 15 % deviation is allowed;
ix. The target delivered dose (ex-actuator) is similar, i.e., 15 % deviation is allowed.

If the formulation differs from that of the comparator product, systemic safety and local tolerance should be demonstrated.

Aerodynamic particle size distributions

In addition to the above listed criteria, the complete APSD profiles determined by using validated multistage impactor or impinger methods should be similar. Statistical assessment of differences should be based on the 90 % confidence interval (CI) preferably at each individual impactor stage or at grouped stages covering not less than four relevant groups. A range of up to ±15% (i.e., 85.0%-115.0% when comparing arithmetic means or 85.0-117.5% when comparing geometric means) is acceptable. Justification is required for higher range and this justification usually requires clinical equivalence data.

Concerning the extent of the *in vitro* comparison, the following aspect should be considered when establishing the APSD profiles: -

i. *Selection of batches:* a minimal number of three batches of the test product consecutively manufactured and three batches of the reference product should be used. Due to the possibility of high variability between batches, (at least) three batches are required to compensate this variability and to provide *in vitro* results that are representative for the commercial product. If there is high variability within or between batches, test a large number of batches (and inhalers per batch) of both the generic product and the comparator product to characterize the variabilities.

ii. *Each strength:* the in vitro studies is performed on each strength proposed for registration, with and without a spacer (if relevant e.g., pMDI). All aspect of the spacers needs to be tested i.e., any spacers recommended in the product information and any spacers described in the product information of the comparator product.

iii. Flow *rates:* in vitro studies should be performed at an acceptable flow rate range (i.e., 30 – 90 L/min) taking into consideration the type of product and patient population. Information on the flow rates, pressure drop ranges and air volumes clinically applicable to the youngest children should be provided.

3.3.5.2 Step 2: Pulmonary deposition studies

If the claim of therapeutic equivalence cannot be supported at the in vitro level, it may be established by demonstrating equivalent pulmonary deposition along with data that support the adequate safety of the test product compared to the reference product. This approach applies to both single API drug products and fixed-dose combination products that contain more than one API. Regarding equivalent pulmonary deposition, two study types, namely pharmacokinetic studies and imaging studies, are generally accepted.

Pulmonary deposition equivalence studies are usually performed in addition to in vitro equivalence studies when the generic product, which contains the same active substance as the comparator product, exhibits differences in excipients, devices, or aerosol performance characteristics of inhalation products. These studies are also conducted if the product fails to meet the criteria of the in vitro studies. For more guidance, please refer to section 6.1 of CPMP/EWP/4151/00 Rev 1.

Pharmacokinetic studies

PK studies are used to measure the pulmonary absorption of the inhaled active pharmaceutical ingredient in the lungs to assess the equivalent efficacy of two drug products. Additionally, PK studies aim to demonstrate that the test product provides comparable systemic exposure and is thus equally safe compared to the reference product.

These PK studies should be conducted in healthy volunteers, although the use of patients is accepted when justified. When performing PK studies, the following aspects should be taken into account:

i. With or without a charcoal block: use a charcoal block if there are data in the published literature that each pharmaceutical ingredient is fully metabolised in the first pass and negligible active ingredient can reach the systemic blood circulation through the gastro-intestinal tract. Studies without active charcoal blockade are sufficient when absorption of the active ingredient in the lung is very quick (e.g., $T_{max} \leq 5$ min) and absorption occurs before the contribution of gastrointestinal absorption is significant (e.g., salbutamol, salmeterol). In this case, AUC0-30 min is usually acceptable as a surrogate for efficacy and AUC0-t for safety;

ii. Use each strength of the medicine: unless the **in vitro** data justify only testing one strength, which is when the **in vitro** results of both the reference product and proposed product are both linear over all the strengths. If only one strength is used, the highest strength is more preferable; and

iii. Dose: at clinically justifiable dose(s) (provide rationale for dose choice): often the highest therapeutic dose allowed for that strength by the product.

Equivalence parameters and criteria

The evaluation of equivalence in PK studies should be based on conventional bioequivalence criteria, which include the maximum or peak plasma concentration (Cmax), the area under the plasma concentration curve (AUC), and the time to Cmax (tmax). For the primary variables, AUC and Cmax, the two-sided 90% confidence interval (CI) of the test product (T) and the reference product (R) ratio T/R should fall within the range of 80.00% - 125.00%.

For highly variable active pharmaceutical ingredients, the confidence limits for Cmax can be widened in line with the requirements prescribed in the Compendium of Guidelines for Marketing Authorization of Human Medicinal Products: part III, section 3.1.8.

Selection of batches

The choice of batches used in the PK studies is critical due to the high variability in aerodynamic particle size distribution between batches of the reference product and changes in PSD and delivered dose during storage.

Before performing the in vivo comparison, representative batches of the test and reference products should be established by testing several batches of both products and selecting batches that are close to the median fine particle dose (or aerodynamic fine particle dose) for each product.

Side batches (batches in the tails of the distribution) representing the test product specifications can also be used in the PK studies, along with side batches of the reference product obtained from the market.

For fixed-dose combinations, different batches can be used for each component if pre-specified in the protocol.

Imaging studies

Lung imaging using gamma scintigraphy with a radiolabeled active pharmaceutical ingredient is another method to demonstrate equivalent lung deposition between the test product and the reference product. These studies aim to quantify the regional lung deposition within different zones of the lungs.

However, it's important to note that imaging studies have limitations when it comes to making equivalence decisions. The current OIP guideline clearly states that these studies cannot replace PK efficacy studies. Instead, the data obtained from imaging studies

should serve as supportive evidence for evaluating therapeutic efficacy and should be complemented by PK studies or clinical studies.

3.3.5.3 Step 3: Pharmacodynamic studies

At the final step of the stepwise approach, pharmacodynamic (PD) studies or clinical studies are necessary when *in vitro* studies and pharmacokinetic (PK) data were insufficient or failed to demonstrate therapeutic equivalence. These studies aim to provide evidence that differences in PK do not affect the safety or efficacy of the test product compared to the reference product.

If the approved indication of the reference product covers both asthma and COPD, therapeutic equivalence studies are only required in one population. It is preferable to conduct these studies in asthma patients as they are easier to carry out.

A key prerequisite for PD efficacy and safety studies is assay sensitivity, which enables the differentiation of the efficacy and safety of treatments or formulations. Sensitivity is confirmed when one of the two studied "non-zero" dose levels demonstrates superiority. Therefore, a minimum of two dose levels should generally be investigated for both products. It is particularly important that these dose levels are investigated in the steep part of the dose-response curve to draw reliable and valid conclusions on the therapeutic equivalence of both products.

In the development of orally inhaled products for use in children, adolescents, and adults, where therapeutic equivalence between two inhaled products must be demonstrated, pharmacokinetic, pharmacodynamic, and/or clinical studies are likely to be required. Such studies may be required across the entire age range of the population, and they may need to be performed separately for each subgroup: less than 2 years, 2-5 years, 6-12 years, and above 12 years. In this case, the design of the PD studies should reflect the target population.

4. CHANGING THE FORMULATION OR DELIVERY DEVICE

When there is a change in the formulation or delivery device of a nasal spray or inhalation medicines, the following should be demonstrated: -

i. The new product is therapeutically equivalent to existing product (when only *in vitro* equivalence data are required) or acceptable comparator product (when lung deposition clinical equivalence data are required); and

ii. The design and principle of operation of the delivery devices for new product and existing product are the same.

4.1 Changes that only require in vitro data

Some changes to the formulation or delivery device, therapeutic equivalence may be demonstrated by using only *in vitro* results: -

i. Use *in vitro* physicochemical methods such as measurement of aerodynamic particle size distribution of the old and new products at several flow rates;

ii. Provide justification for why clinical data are unnecessary if significant physical differences are observed; and

iii. Apply the principles used to determine therapeutic equivalence outlined above.

4.2 Changes that are likely to modify deposition profile

If the deposition profile is likely to be modified by a formulation or delivery device change, it is necessary to provide in vitro physicochemical and lung deposition data, as well as clinical data, to demonstrate the therapeutic equivalence of the new product with the comparator product. The following changes may require such data:

i. Changes to the delivery device that might modify deposition profile; and

ii. Substantial changes to the formulation, such as changing the concentration or buffer of a solution, addition of an agent to modify flow or hygroscopic properties of a powder and removal or substitution of a carrier of a powder.

5. CHANGE HISTORY

Revision No:	Date	Author	Description of change	Section(s) Modified	Approvals
Nil	Nil	Nil	Nil	Nil	Nil

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