Australian Government
Department of Health
Therapeutic Goods Administration

Inhalation and nasal spray registered medicines

Application pathways and data requirements for registration of new generic medicines and variations to existing medicines

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TGA Health Safety Regulation

Contents

1. Introduction

This guidance is for sponsors of inhalation and nasal spray registered medicines (prescription and OTC medicines) and provides guidance on application pathways and data requirements for:

- new generic medicines
- variations to existing medicines

This guidance applies to inhalation and nasal spray medicines that are any of the following:

ü metered-dose asthma inhalers

ü nasal corticosteroids

ü prescription medicines

This guidance does not cover the following dosage forms:

û nasal drops

û sublingual drops

û medicinal gases.

1.1 About inhalation and nasal spray medicines

Nasal spray and inhalation products usually include a delivery device. The site of intended action of the active ingredient may be local or systemic.

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

Inhalation and nasal spray medicines typically have more variable bioavailability than medicines delivered by other routes of administration because of variability in use (e.g. in the patient's inspiratory flow pattern).

1.2 Systemically acting inhalation or nasal spray medicines

Arrange a pre-submission meeting with us if you wish to register a generic of an inhalation or nasal spray medicine that is **systemically acting**. Currently there are very few systemically acting inhalation and nasal spray medicines registered in Australia.

- The guidance below on establishing therapeutic equivalence does **not** apply to systemically acting medicines.
- The intranasal application of a centrally acting agent does not necessarily reflect systemic pharmacokinetics because of potential direct access via the cribriform plate to the central nervous system.

2. Application pathways

2.1 Prescription medicines

Use the prescription medicine registration process if your medicine is a prescription medicine.

2.2 OTC medicines

OTC medicines classed with prescription medicines

Under section 23A of the *Therapeutic Goods Act 1989*, the Secretary may, by notifiable instrument, specify different classes of therapeutic goods for the purposes of section 23B of the Act. Among other things, section 23B sets out certain requirements for applications for registered goods to pass preliminary assessment.

The *Therapeutic Goods (Classes of Therapeutic Goods) Instrument 2018* (made under section 23A) sets out several classes of therapeutic goods. One of the classes of therapeutic goods in the instrument is prescription and other medicines specified in the instrument, including:

- metered-dose asthma inhalers
- nasal corticosteroids

This means that applications under section 23 for these medicines are evaluated as prescription medicines via the prescription medicine process.

If you are unsure of the appropriate application pathway for your inhalation or nasal spray OTC medicine, contact the TGA over-the-counter medicines team.

New registrations

For new registrations of OTC medicines classed with prescription medicines:

- ü Use the prescription medicine registration process, including the appropriate prescription medicine form and paying prescription medicine fees
- ü Use prescription medicine data requirements, including requirements:
  - described in this guidance
  - for providing information on active substance source
- û Do not use prescription medicine labelling requirements
- ü Use OTC labelling requirements, which include requirements for:
  - Product Information
  - Consumer Medicine Information
  - carton and product label
  - any product insert.

Making changes

For changes to OTC medicines classed with prescription medicines:

- Use the appropriate prescription medicine form and pay the prescription medicine fees if your changes include quality-related changes, including changes to:
  - manufacturing
  - formulation
  - quality control
  - container, including container size
  - shelf life
- Use the appropriate OTC medicine form and pay OTC medicine fees if you are only making changes to:
  - labelling
  - Consumer Medicine Information
  - Product Information

OTC medicines that are not classed with prescription medicines

For OTC inhalation and nasal spray medicines that are not classed with prescription medicines, use the OTC medicines registration process and apply OTC data requirements.

The information below about quality, therapeutic equivalence of locally acting medicines and changing the formulation or delivery device does not usually apply to OTC medicines that are not classed with prescription medicines. However, there may be circumstances where some of this guidance is applicable.

3. Quality

3.1 Quality guidelines

The TGA has adopted international guidelines on the pharmaceutical quality of inhalation and nasal medicines:

- Guideline on the pharmaceutical quality of inhalation and nasal products (EMEA/CHMP/QWP/49313/2005 Corr)
- Guideline on stability testing: stability testing of existing active substances and related finished products (CPMP/QWP/122/02, rev1 corr)

For manufacturing batch size and stability studies, inhalation and nasal spray medicines are **critical dosage forms** (except for solutions for nebulisation):

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

Useful information on the quality control of these products is in:

- the BP general monograph for *Preparations for Inhalation*

- USP general monograph <5> Inhalation and nasal drug products—general information and product quality tests
- USP chapter <610> Inhalation and Nasal Drug Products: Aerosols, sprays, and Powders – Performance Quality Tests

3.2 Validation and stability data

Use full commercial scale batches to generate the manufacturing validation and stability data for inhalation and nasal spray medicines, which are critical dosage forms.

3.3 Delivery devices

In this section, 'delivery device' means a device that is supplied as part of the medicine product. We are not referring to separately supplied medical devices, such as spacers and nebulisers.

Use of the delivery device

Provide an illustration of the delivery device of the reference product and the generic product and demonstrate similarity of use.

Rubber or plastic in delivery devices

For the delivery device, in Module 3.2.P.2.4 or 3.2.P.7:

- identify each material, the formulation code and the manufacturer
- include evidence of the biological safety of all components
- provide test certificates or reports to demonstrate compliance if the evidence refers to a monograph in a recognised pharmacopoeia
- 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).

Colour of delivery devices

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

- provide a clinical justification for the colours used
- discuss safety issues around how a user will recognise the difference between different medicines.

Counters

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

- If the reference product has a counter or fill indicator, then a generic product needs to have one too
- If the reference product does not have a counter or fill indicator, then the generic product does not need to have one, although we encourage you to include a counter or fill indicator for all multiple dose inhalation medicines.

Relevant guidance: Guideline on the pharmaceutical quality of inhalation and nasal products (EMEA/CHMP/QWP/49313/2005 Corr) Section 4.2.1.19.

3.4 Information about asthma

For medicines used for preventing or treating asthma, include in:

- Product Information, a link to the Australian asthma handbook <https://www.nationalasthma.org.au/health-professionals/australian-asthma-handbook>
- Consumer Medicine Information, a link to Living with asthma by the National Asthma Council Australia <https://www.nationalasthma.org.au/living-with-asthma>

4. Therapeutic equivalence of locally-acting medicines

Generic medicines evaluated as prescription medicines, need to be of acceptable quality and therapeutically equivalent to an Australian reference product with regard to:

- dosage forms
- strengths
- indications and directions for use

A generic medicine has the same safety and efficacy properties as the Australian reference product (Schedule 9 Part 1 *Therapeutic Goods Regulations 1990*).

4.1 Comparator choice

We strongly recommend that you **use the Australian reference product** in your *in-vitro*, pharmacokinetic and clinical efficacy studies of inhalation products and nasal spray medicines.

If you use an overseas reference product, then you need to demonstrate that the overseas reference product is **identical** (not 'essentially similar') to the Australian reference product. A number of products supplied in Australia are known to be different to those supplied elsewhere in the world, even though they might have the same trade name.

Demonstrating identity is difficult, and requires extensive data including (but not necessarily limited to):

- a deconstruction of the delivery devices to demonstrate identity
- delivered dose data (including delivered dose and delivered volume, spray times, spray pattern and plume geometry, where relevant)
- droplet size distributions: data to demonstrate identity for liquid-based products (such as nasal sprays)
- particle size distribution and morphology of solid and suspended active ingredients: data to demonstrate identity for dry powders (mostly inhalers) and suspensions (nasal sprays and some inhalers), which may be difficult when the active ingredient is only present as a small percentage of a carrier such as lactose
- other physicochemical data (e.g. viscosity, pH, buffer capacity, density, surface tension and osmolality) and quantitative analytical data (with validation data) to demonstrate identity.

4.2 Therapeutic equivalence guidelines

We have adopted international guidelines on establishing the therapeutic equivalence of orally inhaled medicines:

- Guideline on the investigation of bioequivalence (CPMP/QWP/EWP/1401/98 Rev 1/ Corr)
- 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)
- Note for guidance on the clinical requirements for locally applied, locally acting products containing know constituents (CPMP/EWP/239/95)
- 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*

Also of relevance:

- Appendix 1 of Guideline on the pharmaceutical quality of inhalation and nasal products (EMEA/CHMP/QWP/49313/2005 Corr)
- Draft appendix 1 to CPMP/EWP/4151/00, which relates to demonstration of therapeutic equivalence between two inhaled products for use in the management and treatment of asthma in children (EMEA/CHMP/EWP/48501/2008).

4.3 Nasal sprays, metered-dose: therapeutic equivalence

Metered-dose nasal sprays, solutions

Demonstrate that the proposed product and the reference products have the same:

- qualitative and quantitative formulation, as described for inhalation medicine solutions
- droplet size distribution, including data to show the fraction of droplets under 10 micrometres is very small
  - Do not use an impactor that only measures droplets smaller than 12 micrometres, because most of the droplets will be larger than 12 micrometres
- delivered dose and delivered volume
- 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 ten micrometres. This prevents unwanted deposition in the lower airways.

- Show 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

- You may be able to demonstrate that smaller droplets deposit in the nasal cavity, 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 fifty micrometres for nasal spray solutions or suspensions. This gives good distribution in the nasal area and slow clearance.

Metered-dose nasal sprays, suspensions

Obtain all the information required for metered-dose nasal spray solutions.

Demonstrate that the proposed products and the reference products have the same solid state properties:

- particle size distributions of the suspended drug substance within the droplets
  - If any of the excipients are also in suspension, the test method will need to be able to distinguish between particles of the drug substance and particles of excipients
- morphology of the particles of drug substance within the droplets

Examples of methods that are appropriate for some products:

- laser diffraction
- optical microscopy (with or without a polarising filter or a dye, which can often distinguish between drug substance and carrier)
- Raman microscopy
- scanning electron microscopy, with or without energy-dispersive X-ray spectroscopy (EDS), which can often distinguish between drug substance and carrier.

4.4 Nebulised medicines: therapeutic equivalence

Solutions for nebulisation

For solutions for nebulisation, demonstrate that the proposed product has the same qualitative and quantitative formulation as the reference product. Clinical data are required if the formulations are not the same.

- Justify the clinically important physicochemical properties. These are likely to include, but may not be limited to:
  - pH
  - buffer capacity
  - density
  - surface tension
  - viscosity
  - osmolality

- Analyse the reference product formulation and data to show the physicochemical properties of the proposed solution and reference solution are the same
- Provide details and validation data for the non-compendial test methods used.

Suspensions for nebulisation

For suspensions for nebulisation, demonstrate that the proposed product and the reference product have the same:

- qualitative and quantitative formulation, as described for solutions for nebulisation
- particle morphology of the drug substance in the suspension
- particle size distribution of the drug substance in the suspension:
  - The test method needs to be able to distinguish between particles of the drug substance and particles of excipients if any of the excipients are also in suspension
- droplet size distribution of the nebulised droplets
  - Use appropriate methods to test droplet size

4.5 Inhalation medicines, metered-dose: therapeutic equivalence

For metered-dose inhalation medicines, establish therapeutic equivalence in a stepwise manner.

Establishing therapeutic equivalence

In order to demonstrate therapeutic equivalence, clinical trials are in principle necessary.

For locally-acting inhalation medicines, you can establish therapeutic equivalence stepwise:

1. *in vitro* equivalence studies—there are some situations in which these studies are sufficient
2. lung deposition equivalence studies—usually it is necessary to perform these studies in addition to *in vitro* equivalence studies
3. clinical efficacy equivalence studies—required when you cannot establish therapeutic equivalence of inhalation medicines using *in vitro* or lung disposition methods. You may also use them as supportive evidence in addition to the *in vitro* or lung disposition methods.

All methods used must be adequately validated.

You need to establish that your generic medicine has the **same safety properties** as the Australian reference product. If the formulation differs from that of the reference product, you need to address systemic safety and local tolerance. Usually you can obtain this data in the same study as lung deposition equivalence or clinical equivalence.

In vitro equivalence

Section 5.2 of CPMP/EWP/4151/00 Rev 1 outlines when *in vitro* data are sufficient to establish therapeutic equivalence for metered-dose inhalation medicines. The requirements below are primarily for suspensions. You may need less data for solutions.

Each strength

Perform *in vitro* studies on each strength proposed for registration, with and without a spacer (if relevant e.g. pressurised metered dose inhalers). All of the following spacers need to be tested:

- any spacers you are going to recommend in the Product Information of your product
- any spacers described in the Product Information of the Australian reference product.

Flow rates

Perform *in vitro* studies at a range of flow rates:

- take into account the type of product and patient population
- include flow rates, pressure drop ranges and air volumes clinically applicable to the youngest children allowed in the Product Information.

Aerodynamic particle size distributions

Meet each of the criteria outlined in the EU Guidance CPMP/EWP/4151/00 Rev 1. The TGA provides the following additional guidance.

Determine aerodynamic particle size distributions using an appropriate method:

- Next Generation Impactor (NGI) is preferred
- Andersen Cascade Impactor (ACI) may be acceptable with a justification

When determining the aerodynamic particle size distributions:

- Use a minimum of 3 batches of both the generic product and the reference product (CPMP/EWP/4151/00 Rev 1). However, more batches are usually required: see below
- 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 reference product to characterise the variabilities
  - Take enough measurements at the beginning, middle and end of the shelf life of each batch (this may be up to 10 measurements at each time for each batch)
  - Test sufficient batches (**this may need to be 6-10 batches or more**)

Provide the results for each stage of the impactor, as well as for any predefined groups of stages.

- Perform a comparison on each stage
- Perform a comparison on each group of stages (minimum of 4 groups) and include a justification for the groups based on clinical arguments (for more information go to CPMP/EWP/4151/00 Rev 1)
- For the 90% confidence intervals for the comparison of the stages (or groups of stages), we will accept 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). You need to justify any higher range and this justification usually requires clinical equivalence data.

Lung deposition equivalence

Lung deposition studies investigate the extent and pattern of pulmonary deposition of an inhaled active substance. Section 6.1 of CPMP/EWP/4151/00 Rev 1 provides guidance on lung deposition studies.

Choice of batches

How you choose the batches tested in the pharmacokinetic studies is very important:

- variability in aerodynamic particle size distribution between batches of the reference product may be high
- particle size distribution and delivered dose of some products change on storage

Before performing the *in vivo* comparison, find representative batches of the test and reference products by:

- testing several batches of the test and reference products
- choosing batches that are close to the median fine particle dose (or aerodynamic fine particle dose) for that product

You might also perform pharmacokinetic studies using side batches (batches in the tails of the distribution) representing the test product specifications against side batches of the reference product obtained from the market.

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

Pharmacokinetic studies

Pharmacokinetic studies are the most common way that lung deposition equivalence is established. These are usually conducted in healthy volunteers, although occasionally there may be a clinical reason why it is more appropriate to use patients.

Perform pharmacokinetic studies:

- with and without a charcoal block
  - You do not need to use a charcoal block if there are data in the published literature that each active 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, $AUC_{0\text{-}30\ min}$ is usually acceptable as a surrogate for efficacy and $AUC_{0\text{-}t}$ for safety.
- 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 you use only one strength, use the highest strength
  - for more information go to CPMP/EWP/4151/00 Rev 1 Section 4.5
- at clinically justifiable dose(s) (provide rationale for dose choice):
  - often the highest therapeutic dose allowed for that strength by the Product Information
  - for more information go to CPMP/EWP/4151/00 Rev 1

Results required for therapeutic equivalence

We consider therapeutic equivalence to be established if:

- the 90% confidence intervals for the geometric mean ratios of C_{max} and AUC_{0-t} are within the range 80.00 to 125.00%
  - For highly variable drug substances, the confidence limits for C_{max} can be widened in line with subsection 4.1.10 of CPMP/QWP/EWP/1401/98 Rev 1/ Corr, but you must perform a replicate study to establish that the drug substance is highly variable
- there is no difference in the median and range of T_{max}, because T_{max} is dependent on the sites of absorption within the lung; there is no formal requirement for the calculation of confidence intervals for T_{max}.

Clinical efficacy equivalence

Clinical studies are usually only supportive of *in vitro* or lung disposition equivalence and are often **unable to establish** therapeutic equivalence.

For clinical efficacy equivalence studies, see:

- general guidance in section 6.2 of CPMP/EWP/4151/00 Rev 1 (adopted in Australia)
- the following US FDA draft guidance, not adopted in Australia, specific to the following:
  - budesonide
  - fluticasone propionate and salmeterol xinafoate.

5. Changing the formulation or delivery device

When you change the formulation or delivery device of a nasal spray or inhalation medicine regulated as a prescription medicine, demonstrate that

- the new product is therapeutically equivalent to:
  - your current registered product, when only *in vitro* equivalence data are required
  - the Australian reference product (innovator), when lung disposition or clinical equivalence data are required
- the delivery devices look and handle the same.

5.1 Changes that only require *in vitro* data

For some changes to the formulation or delivery device, you may be able to demonstrate therapeutic equivalence using only *in vitro* results:

- use *in vitro* physicochemical methods such as measurement of aerodynamic particle size distribution of the old and new products at several flow rates
- provide justification for why clinical data are unnecessary if significant physical differences are observed
- apply the principles used to determine therapeutic equivalence outlined above.

5.2 Changes that are likely to modify disposition profile

If the disposition profile is likely to be modified by the formulation or delivery device change, then you require *in vitro* physicochemical and lung disposition and/or clinical data to demonstrate therapeutic equivalence of the new product with the Australian reference product.

Such changes include:

- changes to the delivery device that might modify disposition profile
- 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
  - removal or substitution of a carrier of a powder.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication: Guidance 19: Inhalation and nasal medicines – previously ARGPM Appendix 19: metered dose aerosols [pressurised and non-pressurised]	Office of Medicines Authorisation	09/08/2013
V2.0	Title and scope changed Removed guidance irrelevant to new scope Increased information about application pathways Clarified how to establish therapeutic equivalence Restructured to increase readability	Scientific Evaluation Branch with the Regulatory Guidance Team	May 2018
V2.1	Added information to section 1.2 'Systemically acting inhalation or nasal spray medicines'	Scientific Evaluation Branch	October 2019

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
https://www.tga.gov.au

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