Guidance 19: Inhalation and nasal medicines
Previously ARGPM Appendix 19: Metered dose aerosols [pressurised and non-pressurised]

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Check the TGA website for up-to-date guidance

The most up-to-date information about prescription medicine registration in Australia is on the TGA website <http://www.tga.gov.au>. Now that guidance is presented in a series of web pages, updates are likely to be more common than in the past. If you subscribe to the TGA guidelines email alert service, you will be emailed every time the TGA web guidance is updated.

TGA web pages are dated, and can be printed.

A PDF format is being provided during the transition between the former version of the ARGPM (Australian Regulatory Guidelines for Prescription Medicines) and the new web format. Please note that information in the PDF should not be relied upon to be up-to-date.

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.

- The TGA administers the Therapeutic Goods Act 1989 (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.

- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.

- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.

- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.
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Introduction

This guidance describes the data requirements to support:

- applications to register new inhalation and nasal medicines
- applications to register generic inhalation and nasal medicines
- requests to vary registered inhalation and nasal medicines.

19.1 What are inhalation and nasal medicines

**Inhalation and nasal medicines** include medicines for:

- treating asthma
- chronic obstructive pulmonary disease (COPD), and
- other conditions of the lung (including cystic fibrosis).

Related information and guidance

- Guideline on the pharmaceutical quality of inhalation and nasal products (EMEA/CHMP/QWP/49313/2005)
- Guideline on clinical investigation of medicinal products in the treatment of patients with acute respiratory distress syndrome (EMEA/CPMP/EWP/504/97 Rev 1)
- Points to consider on clinical investigation of medicinal products in the treatment of patients with chronic obstructive pulmonary disease (COPD) (CPMP/EWP/562/98)
- Guideline on the clinical development of medicinal products for the treatment of cystic fibrosis (EMEA/CHMP/EWP/9147/2008)
- Guideline on the clinical development of medicinal products for the treatment of allergic rhino-conjunctivitis (CHMP/EWP/2455/02)
- Note for guidance on the clinical investigation of medicinal products in the treatment of asthma (CPMP/EWP/2922/01)

19.1.1 What is the evaluation pathway for inhalation and nasal medicines

Generally, over-the-counter (OTC) nasal sprays for local effect, such as nasal decongestants or products for allergy/hayfever relief, are evaluated via the OTC medicine route.

Some inhalation and nasal medicines supplied OTC, such as asthma inhalers and corticosteroid nasal sprays, have specialised requirements for clinical and quality data and are routinely evaluated via the prescription medicines registration process.
19.2 Clinical requirement for generic metered-dose aerosols

Generic medicines are expected to be of acceptable quality and clinically interchangeable with an innovator medicine with regard to:

- dosage form(s)
- strengths
- indications and directions for use.

A clinical study will be necessary to demonstrate equivalent performance, unless the application demonstrates the formulation is identical to the innovator medicine (e.g. using the same solutions for nebulisation).

**Note**
The design of the study is the responsibility of the sponsor of the generic medicine.

19.2.1 Selecting a reference medicine

In Australia, most single-agent and all fixed-combination inhaled pulmonary medicines used in asthma and COPD are innovator medicines. It is therefore preferable to select an Australian marketed innovator medicine with which to compare the generic medicine.

In the application:

1. provide the clinical data described in the sections below
2. include the studies for the Australian-sourced innovator medicine as the reference medicine.¹

**Note**
Using a foreign-sourced reference medicine increases concern about clinical interchangeability.

Information in the guidance Biopharmaceutic studies about selecting a reference product does not apply to inhalation and nasal medicines.

See the TGA's annotation concerning Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1), which states:

'The procedure for abridged applications claiming essential similarity to a reference product (i.e. generics), which allows applications to be made to numerous Member States of the EU, based on bioequivalence with a reference product from one Member State, does not apply in Australia. An application for registration of a generic product in Australia should generally include a bioequivalence study versus a leading brand obtained in Australia'.
19.2.2 The performance of aerosols and demonstrating equivalence

The performance of aerosols is critically dependent on the particle size distribution of the medicine. However, physical data on aerosol particle size distribution are insufficient on their own as a basis for judging equivalence, because other factors are also important – specifically:

- the excipients present (including the propellant gases and their partial pressures)
- the dispersing agent and the valve and metering system in the container.

For example, by changing the dispersing agent, it is possible to slow the pharmacokinetic clearance of the medicine from the lungs, to such an extent that a sustained release aerosol is produced.

It is also of value to determine the relative sites and extents of deposition of the medicine in the respiratory tract for the generic product and the innovator product.

Section 5.2 of the guideline adopted from the European Medicines Agency (EMA), 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), sets out a number of matters for consideration.

The guideline states, 'If the product does NOT satisfy ALL of these pharmaceutical criteria for equivalence, in vivo studies should be performed to substantiate equivalence'.

However, the pharmaceutical criteria listed in the guideline are more usefully applied to different strengths of an inhaled medicinal product - for example, to justify not studying all strengths – than to establishing similarity of a generic medicinal product to a reference product.

19.2.3 Minimum data requirements for Generic beta-2 agonists and anticholinergics

The minimum data required are a comparison of the bronchodilator effect of the proposed generic medicine and a leading Australian registered medicine, using measurements of FEV1 (forced expiratory volume in 1 second) and/or FEV1 area under the curve in mild to moderate asthmatics.

Challenge tests alone, such as histamine provocation or exercise, are insufficient to confirm equivalence of beta-2 agonist performance, but could be used to support clinical studies on the bronchodilator effect.

Studies should be randomised, double-blind, crossover comparisons of the products in stable asthmatics who showed a bronchodilator response of at least 200 mL in FEV1 or 60 L/min in peak expiratory flow.

Subjects participating in the study should be shown to be stable for at least 4 weeks before the study – that is, their level of symptoms and medication should be constant, and they should be otherwise healthy. The protocol should include guidelines on the continuation or modification of other medication.

Slow-release theophylline should be withheld for at least 24 hours before the study. Inhaled bronchodilators should be withheld for a sufficient time to ensure that there is no carryover effect between study days.
The stability of FEV1 between study days should be assured (±15 per cent or less is preferable). On the study day, the subjects' baseline spirometry should be consistent for 30 minutes before the study begins. Administration of medication in addition to the study medicines should be standardised for both study days.

Normally, the area under the curve for FEV1 should be measured for a sufficient time to fully define each response curve. Extrapolation to infinite time is not necessary. Provided the baseline is sufficiently tightly controlled, it would be adequate to base the comparison of the two products on the absolute values measured.

If the study shows no difference in efficacy, and the propellants and dispersing agents or other excipients in the generic product are not new (i.e. they are present in another aerosol product registered in Australia), no further clinical studies need to be performed. If differences in efficacy are shown, the product is not a generic medicine.

Sponsors are encouraged to submit results from additional comparisons of the products using provocation or challenge tests, but this is not a requirement.

Australian 'reliever' inhalers should be presented in blue actuators.

### Related information and guidance

- Asthma management handbook 2006

### 19.2.4 Generic non-corticosteroid prophylactics

A clinical study is required for products containing medicines used for the prophylactic treatment of asthma by inhibiting the release of mediators of the allergic reaction from effector cells.

This study might include an appropriate challenge test, such as exercise, that compares the effect of the proposed product with a leading Australian product.

Provided that this study shows equivalent performance, and the aerodynamic characteristics of the products are comparable, no further studies are required.

If the acute study shows a difference in effect, long-term comparison of clinical efficacy, or a study comparing the in vivo deposition profile of the generic aerosol with the reference product, is required.

The results of such bioassays are inherently more variable for these medicines than for bronchodilators, and the TGA will take this into account in deciding what constitutes an acceptable difference, on the basis of the available discriminatory power.

### 19.2.5 Statistical requirements for clinical trials on generic beta-2 agonists, anticholinergics and non-corticosteroid prophylactics

For clinical trials to compare two similar metered-dose aerosols in this group, such as two beta-2 agonist aerosols, the confidence interval approach is an appropriate form of statistical analysis.
In general, two products may be considered clinically equivalent if their effect does not differ by more than 20 per cent – that is, if the chosen confidence interval for the effect ratio of generic to reference product falls within the range 80-120 per cent.

However, the confidence interval range of 80-120 per cent may not always be appropriate for clinical studies outlined under **Generic non-corticosteroid prophylactics** because of the inherently greater variability in such studies.

The sponsor should justify any confidence interval other than 80–120 per cent.

### 19.2.5.1 Generic corticosteroids

For corticosteroids, a comparative efficacy study with a leading Australian product that incorporates appropriate monitoring of adverse effects is required:

- Physical data on aerosol particle size distribution are required as part of the application, but are insufficient alone to demonstrate product equivalence.
- Studies may include a crossover substitution design or a parallel group design. Parallel designs give lower statistical power and require greater patient numbers.

Since it is common to use spacer devices with metered-dose aerosols containing corticosteroids (to reduce oropharyngeal deposition of the medicine while maintaining efficacy), clinical studies should be conducted with any spacer device recommended in the product information for use with the proposed generic medicine.

If a spacer device was not used in these studies, promotion of a spacer for use with the product will require supporting data.
19.3 Special requirements for nasal metered-dose aerosols

Make a clear distinction between products containing medicines intended for systemic absorption when given by the nasal route and products intended to produce local effects.

Quality assurance procedures for nasal metered-dose aerosols are different from those for aerosols delivered by oral inhalation – for example, a cascade impactor that measures particles smaller than approximately 12 micrometres would not be useful for nasal aerosols.

Either the particle size distribution of the aerosol cloud produced by the proposed product should be shown to be appropriate for nasal administration, or data should be presented to show the proportion of the dose that is deposited in the nose.

19.3.1 Medicines intended for systemic absorption

Define the *in vivo* bioavailability of the drug substance from the proposed medicine.

Because of the very high initial velocity of particles from a pressurised aerosol, the anatomy of the nose and the turbulence of the airflow, the great majority of particles delivered by each valve actuation will deposit in the nasal area and may elicit a local effect.

Extensive data are available on the nasal administration of medicines, with regard to deposition and clearance.

The optimal particle size for nasal deposition is approximately 50 micrometres, which gives good distribution in the nasal area and slow clearance.

19.3.2 Medicines intended for local effects

The particle size of the aerosol generated by the delivery device should generally be more than 20 micrometres, to prevent unwanted deposition in the lower airways.

Because the velocity and direction of the aerosol cloud also affect deposition, the sponsor may show by *in vitro* or *in vivo* testing that the method of administration causes even smaller particles to deposit in the nasal cavity.

An alternative to comparative assessment of the biological activity of generic and reference products intended to produce a local effect is measurement of the residence time of the medicine in the nose. This is the preferred approach. It can be achieved using a gamma-camera and radiolabeled medicinal product, or chemically after nasal lavage.
19.4 Other inhalation medicines to treat pulmonary conditions

Pharmacokinetic and pharmacodynamic interactions with concomitant medications should be explored.

Related information and guidance

- Note for guidance on dose response information to support drug registration (CPMP/ICH/378/95) for the required dose-finding information

Note

Special attention to local adverse effects is required.
19.5 Other inhalation and nasal medicines that deliver drug substances

19.5.1 Delivery of medicine directly to the lung

Delivering a medicine directly to the lung can sometimes be advantageous - for example, use of dornase alfa and tobramycin in cystic fibrosis. In these conditions:

- demonstrate adequacy of pulmonary deposition in healthy volunteers and also in patients with the condition, including patients with moderate to severe lung disease.
- explore pharmacokinetic and pharmacodynamic interactions with concomitant medications.
- provide dose-finding information.

Related information and guidance

- 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 dose response information to support drug registration (CPMP/ICH/378/95). Special attention to local adverse effects is required.

19.5.2 Delivery of medicine for systemic exposure

Drug substances can be administered via the intranasal or pulmonary routes to achieve systemic exposure. For example:

- salcatonin administered intranasally.

In such cases:

- characterise pharmacokinetics
- determine absolute bioavailability
- explore pharmacokinetic and pharmacodynamic interactions with concomitant medications
- explore the effects of smoking
- provide dose-finding information.

Related information and guidance

- Note for guidance on dose response information to support drug registration (CPMP/ICH/378/95)
Note

Special attention to local adverse effects is required. In addition, long-term effects on lung function must be studied when the pulmonary route is used.
19.6 Pharmaceutical requirements for inhalation and nasal medicines

19.6.1 Presentation of asthma reliever medicines in Australia

Asthma reliever medicines in Australia are presented in blue actuators.

There are significant safety issues that should be addressed in the application if a proposed generic medicine does not use an appropriate actuator.

Related information and guidance

• Asthma management handbook 2006
• Guideline on the pharmaceutical quality of inhalation and nasal products (EMEA/CHMP/QWP/49313/2005)

19.6.2 Rubber or plastic components

Substances leached from rubber or plastic material contained in metered-dose aerosol containers as valve components or gaskets may cause adverse effects.

In the application:

• identify the material, formulation code and manufacturer
• include evidence of the biological safety of such components
• provide test certificates or reports to demonstrate compliance where this evidence refers to a monograph of a recognised pharmacopoeia (e.g. United States Pharmacopeia (USP) <87>).

19.6.3 Stability data

Inhalation and nasal medicines (other than solutions for nebulisation) are 'critical dosage forms' for the purposes of Guideline on stability testing: stability testing of existing active substances and related finished products (CPMP/QWP/122/02, rev 1).
19.7 Variations to registered inhalation and nasal medicines

19.7.1 Changes to the quality aspects of registered aerosols
Where appropriate, provide a rationale for proposed changes to the quality aspects of registered aerosols.

The degree of change can vary from:

- major change, such as a change in valve size or design
- minor change, in the content of propellant that has minimal effect on the partial pressure of the mixture.

19.7.1.1 For minor change
To demonstrate equivalence of performance:

- physicochemical methods, such as measurement of mass aerodynamic particle size distribution of the new and old products, will normally be sufficient to demonstrate equivalence of performance.

Note
Provide either a clinical study or a justification for why a clinical study is unnecessary, if:

- there is a difference in physical performance
- the change is likely to cause a difference in particle size distribution or clinical effect.

Related information and guidance

- Minor variations to registered prescription medicines: Chemical entities

19.7.2 Changes to powders for inhalation

19.7.2.1 Changes to the delivery device
Changes to the delivery device can have a major influence on the deposition profile of an inhaled powder.

Thus, a change to its design or method of operation would normally cause the modified system to be a new medicine and would require full clinical and physicochemical data.
19.7.2.2 A substantial change in the formulation of the inhaled powder

A substantial change in the formulation of the inhaled powder such as addition of an agent to modify its flow or hygroscopic properties removal or substitution of carrier, will require a full dataset, since the deposition profile could change markedly.

19.7.2.3 A minor change to an excipient in a registered powder or minor changes to the delivery device

Physical measurements, such as mass aerodynamic particle size distribution of the delivered aerosol, are usually sufficient to support minor changes in the content of an excipient in a registered powder for inhalation, or minor changes to the delivery device.

- Generate these data at several flow rates.
- Provide either clinical data or a justification for why such data are unnecessary if significant physical differences are observed.
- Encompass the principles outlined under Clinical requirements for generic metered-dose aerosols for any clinical study performed to support a change to a powder for inhalation.