



MEDSAFE

NEW ZEALAND MEDICINES
AND MEDICAL DEVICES
SAFETY AUTHORITY

A BUSINESS UNIT OF
THE MINISTRY OF HEALTH

New Zealand Regulatory Guidelines for Medicines

Part A:

**When is an application for approval
of a new or changed medicine required?**

**Edition 6.16
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(consolidation of fifth edition and subsequent updates)

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[Link to List of Abbreviations](#)

Section 1: Therapeutic Products Controlled under New Zealand Legislation

Section summary

The medicines legislation controls products used in humans for a therapeutic purpose.

Products used for a therapeutic purpose can be categorised as medicines, related products, herbal remedies or medical devices. These terms are explained in this section.

A product is considered to be intended for a therapeutic purpose if a therapeutic claim is stated or implied in the product labelling or promotional material, or where the active ingredient(s) clearly has a pharmacological action. This section describes the sorts of statements considered to be therapeutic claims.

Legislation to read in conjunction with this section:

Medicines Act 1981

Section 2: Interpretation and meaning of 'medical device'

Section 3: Meaning of 'medicine', 'new medicine', 'prescription medicine' and 'restricted medicine'

Section 4: Meaning of 'therapeutic purpose'

Section 28: Exemptions in respect of herbal remedies

Section 94: Meaning of 'related product'

Part IV: Medical advertisements

Dietary Supplement Regulations 1985

Regulation 2: Interpretation

Regulation 11: Therapeutic claims

1.1. Medicines

The term "medicine" is defined in [Section 3](#) of the [Medicines Act 1981](#). In practical terms, a product is a medicine if it is administered to humans primarily for a therapeutic purpose. Most, but not all, medicines have a pharmacological effect. Therapeutic purpose is defined in [Section 4](#) of the Act, and includes the treatment, diagnosis and prevention of disease or the modification of a physiological function. It also includes cleaning, soaking or lubricating contact lenses, inducing anaesthesia, or effecting contraception. Spermicidal condoms and intrauterine devices (IUDs) containing copper or a hormone are medicines whereas non-spermicidal condoms and other barrier-type contraceptives (eg, diaphragms) are devices. *In vivo* diagnostic agents are medicines while *in vitro* diagnostic products are devices (with the exception of pregnancy test kits which are medicines). The only products that are regulated as medicines, but are not actually administered to humans, are pregnancy test kits. The consent of the Minister is required before a new medicine can legally be distributed in New Zealand (except in the case of certain specified exemptions, as explained later in this document).

Medicines that are also **Controlled Drugs** are controlled under the [Medicines Act 1981](#) and associated Medicines Regulations and also the [Misuse of Drugs Act 1975](#) and associated Misuse of Drugs Regulations.

In accordance with [Section 109\(4\)](#) of the Medicines Act, where a product is controlled under both sets of legislation, the Misuse of Drugs legislation takes precedence in the event of any inconsistency.

1.2. Related Products

A related product is a product that is primarily a food, dentifrice or cosmetic, but has a secondary therapeutic use. This term is defined in [Section 94](#) of the Medicines Act. The consent of the Minister is required before a new related product can legally be distributed in New Zealand. The legislation does not require a related product to be manufactured in a factory licensed to manufacture medicines, but the manufacturer must comply with an appropriate standard of GMP (see [Part D, Section 5](#)).

1.3. Herbal Remedies

A herbal remedy is a special sub-category of medicine, defined in [Section 2](#) of the Medicines Act. A herbal remedy is a medicine that does not contain a prescription, restricted or pharmacy-only medicine, and consists of a substance derived from plant material that has been dried or crushed (or derived through any other similar process). It may also be an aqueous or alcoholic extract of the dried or crushed plant material, or a mixture of that material with another inert substance.

Ministerial consent is not required for the distribution of a herbal remedy which is sold or supplied without any recommendation as to its use and the labelling complies with the requirements of [Section 28](#) of the Medicines Act, whereas Ministerial consent is required for the distribution of a herbal remedy which is sold with a recommendation for use for a therapeutic purpose.

1.4. Homeopathic Remedies

A homeopathic remedy which is prepared under the principle of homeopathy in which the active ingredient to be administered is in a concentration not more than 20 parts per million, and the remedy is labelled only with the name of the active ingredient, trade name (if any) and a statement that it is a homeopathic remedy does not normally require Ministerial consent before distribution. The product label or associated advertising material must not contain therapeutic claims or indications for use.

A homeopathic remedy which is labelled or advertised with claims as to its therapeutic purpose is a medicine and subject to the full control of the Medicines legislation.

Sterile homeopathic preparations intended for injection or for administration to the eyes are regarded as medicines and therefore subject to the full control of the Medicines legislation

1.5. Medical Devices

Superseded. Please refer to the 'Devices' section of the Medsafe website for information about the regulation of medical devices including definitions, regulation and standards <http://www.medsafe.govt.nz/devices/devices-landing.asp>

1.5.1. Clinical trials involving medical devices

Superseded. Please refer to [Part 11](#) of the *Guideline on the Regulation of Therapeutic Products in New Zealand*.

1.6. Cosmetics with a Therapeutic Purpose

[Section 2](#) of the Medicines Act 1981 defines a cosmetic. In general terms, a cosmetic is a product used to cleanse, protect or beautify the hair or skin. The following types of products, when sold without any therapeutic claims and not containing any substance listed in the [First Schedule](#) of the [Medicines Regulations 1984](#) (and amendments) are considered to be **cosmetics**, and the Minister's consent for distribution is not required for their distribution:

- ☞ Antiperspirants
- ☞ Deodorants
- ☞ Insect repellents
- ☞ Dusting powders
- ☞ Sunscreen and suntan preparations
- ☞ Cleansers for normal or blemished skin
- ☞ Moisturisers for normal, sunburnt or wind burnt skin
- ☞ Hair conditioners
- ☞ Astringents and skin toners
- ☞ Agents to assist in the fading of spots, pimples and blemishes
- ☞ Antiseptics for generalised, all-over use, on the body and not on broken skin
- ☞ Solutions which are bathed in to relax the body
- ☞ Anti-wrinkle and anti-ageing products which have a superficial cosmetic effect and not a physiological effect.

Cosmetics must not be advertised as making basic underlying changes to the skin such as cellular changes.

Sunscreens are currently categorised as cosmetics and do not require approval or Ministerial consent before marketing. Companies are encouraged to market only sunscreens that comply with the [Australian/New Zealand Standard AS/NZS 2604:1998 Sunscreen Products - Evaluation and Classification](#). Companies marketing sunscreens should have evidence to support the SPF and broad spectrum protection claimed. Future legislation may control sunscreens as therapeutic products.

1.7. Radiopharmaceuticals

Radiopharmaceuticals are not controlled under the Medicines Act or Medicine Regulations administered by Medsafe. Control of the import and use of radiopharmaceuticals in New Zealand is the responsibility of the [Office of Radiation Safety](#) (ORS).

Anyone intending to import radioactive materials into New Zealand must have the consent of the Team Leader ORS. Any hospital, clinic or medical practitioner intending to administer radiopharmaceuticals to a patient or patients for the purpose of diagnosis or treatment must be licensed to do so by the ORS. Further information may be obtained from the website of the ORS <http://www.health.govt.nz/our-work/radiation-safety>

1.8. Dietary Supplements

Dietary supplements are controlled under the [Dietary Supplement Regulations 1985](#). [Regulation 2](#) of these Regulations defines a dietary supplement. In practical terms, a dietary supplement is an edible substance, in a controlled dosage form, which is intended to supplement the intake of substances normally derived from food. A product marketed as a dietary supplement may not be promoted for a therapeutic purpose. Companies wishing to make therapeutic claims for such products must apply for consent to distribute the product as a medicine or related product.

1.9. Categorisation by Substance or Product Type

If a product is administered to humans and contains a substance that exerts a therapeutic effect, that product is considered to be a medicine, irrespective of whether therapeutic claims are made on the label or in advertising material. For example, a product containing a hormone is a medicine, regardless of the purpose for which it is being promoted.

The [First Schedule](#) of the [Medicines Regulations 1984](#) contains a list of Prescription, Restricted and Pharmacy-Only Medicines. It also contains some “class” classifications (eg, anorexiant). The First Schedule is therefore a useful guide to determining whether or not a product is considered to be a medicine. However, please note that listing of a particular medicine in the First Schedule does not necessarily mean that it is currently approved for distribution in New Zealand, but rather, that it would be classified as indicated if it was approved for distribution.

1.10. Therapeutic Purpose and Claims

There may be several indicators that a product has a therapeutic purpose. These may include:

- ☞ the trade name of the product conveying an intended purpose
- ☞ use of the words *remedy*, *medicated* or *therapeutic*
- ☞ statements of historical therapeutic use, or use by ethnic groups for a therapeutic purpose
- ☞ directions for use, such as *Spread on affected area*
- ☞ use of statements to the effect that the manufacturers are prohibited from making specific claims about the product.

A therapeutic claim can be direct, implied, or suggested. Statements that a product will/can/may/is intended to give relief from a disease, pain, or symptoms associated with a disease are therapeutic claims.

Nutritional statements, or statements relating to the normal biochemical or physiological function of a substance, are not considered to be therapeutic claims.

The following is a guide to the sorts of claims made for products.

Gastro-intestinal system

A claim such as *Beneficial for the digestive tract. Good for abdominal cramps* is regarded as a therapeutic claim, since it implies or indicates treatment for an adverse physiological condition. If *Good for abdominal cramps* were removed, the product would not be considered a therapeutic product.

A claim such as *Supports the healthy function of kidneys, liver and digestive tract* is regarded as a broad statement relating to normal biochemical function, hence the product would not be considered a therapeutic product. A claim such as *Beneficial for digestion and intestinal complaints. Use for cholesterol control* is regarded as a therapeutic claim, both because the

product is implied/intended for the alleviation or treatment of intestinal complaints, and because it is intended to reduce cholesterol.

A claim such as *For the formation of a number of important biological substances required for many vital cellular functions* would be regarded as a broad statement relating to nutritional needs, and not a therapeutic claim.

Urinary system

A claim such as *Helps maintain the healthy function of urinary organs. Has anti-inflammatory properties* is considered to be a therapeutic claim since it implies that maintenance is by means of the anti-inflammatory properties of the product.

A claim such as *Beneficial for the genito-urinary system. Use for fluid retention* is regarded as a therapeutic claim since it is implied the product treats fluid retention. If the sentence *Use for fluid retention* is removed, the claim would fall into the category of a statement relating to normal biochemical or physiological function.

Cardiovascular system

A claim such as *Anti-thrombotic, cholesterol-suppressive* for an edible product is regarded as a therapeutic claim because the product would be marketed for these purposes, rather than for its nutritional purpose.

Respiratory system

A claim such as *Beneficial and soothing for the respiratory system. Alleviates mucous congestion* is regarded as a therapeutic claim, since the product is implied or intended to relieve a particular symptom of an adverse physiological condition.

Central nervous system

A claim such as *Temporary relief of sleeplessness and excitability* is considered to be a therapeutic claim since the product is principally intended to act as a sedative, and would not have a nutritional purpose.

Musculoskeletal system

A claim such as *Beneficial for the temporary relief of pain due to arthritis, rheumatism, menstruation and muscular pain* is regarded as a therapeutic claim. Generally, all products intended to be analgesics, or acting by means of an analgesic effect, are therapeutic products.

Obstetrics and gynaecology

A claim such as *Apply for nappy rash* or *Apply to cracked nipples* is regarded as a therapeutic claim since the product would purport to relieve these physiological conditions.

Eye, ear, nose, mouth and throat

A claim such as *Removes problem-causing bacteria which cause bad breath* or *Removes plaque* would not normally be considered to be a therapeutic claim unless the product is also intended to treat conditions such as gingivitis.

A claim such as *Relieves sore throats* or *Soothes sore throats* for a lozenge is regarded as a therapeutic claim because an anaesthetic action is involved.

Skin

A claim such as *Disinfection of hands and skin* would not be regarded as a therapeutic claim. Conversely, a claim such as *For the prevention of infection in wounds, cuts and abrasions* is a therapeutic claim because the product would be applied to broken skin.

A claim such as *Keeps skin smooth and resilient* would not be regarded as a therapeutic claim.

A claim such as *Removes oil, make-up and dirt without over-drying. Medicated to kill problem-causing bacteria* would not generally be regarded as a therapeutic claim in spite of the use of the word 'medicated', unless the product is intended to be used or has an implied use on a specific skin condition.

A claim such as *Promoting hair growth* or *Increasing nutrient supplies for follicles* would be regarded as a therapeutic claim, since baldness and its associated physiological condition is listed in the [First Schedule to the Medicines Act 1981](#).

1.11. Requirements to Comply with Other Legislation and Standards

1.11.1. Consumer legislation

Medicines, related products and medical devices are regulated by the [Ministry of Health](#) in accordance with the Medicines and Misuse of Drugs legislation. Sponsors should also be aware that, as these products are articles of commerce, they also need to comply with any other relevant consumer legislation (eg, [the Fair Trading Act 1986](#)) administered by the [Ministry of Economic Development](#).

1.11.2. Hazardous Substances and New Organisms legislation

Certain medicines must comply, not only with the Medicines legislation, but also with the requirements of the [Hazardous Substances and New Organisms Act 1996](#) (HSNO), its amendments and its associated regulations as administered by the [Environmental Protection Agency New Zealand](#) (EPA).

Most human medicines in finished dose form are exempt from the HSNO legislation even when they cross the HSNO thresholds for hazardous properties. However, the following types of new human medicines are *not exempt* and must comply with the HSNO legislation:

- ☞ Substances that are gases (eg, medical gases) contained in pressure containers of more than 100 mls **and** at pressures of more than 170 kPa, up until the time they are administered to one or more human beings for a therapeutic purpose.
- ☞ New medicines (eg, vaccines or gene therapy products) that contain live or attenuated viruses or bacteria and are "new organisms" as defined in [section 2\(A\) of the HSNO Act 1996](#). To be a new organism it must be "a species of any organism which was not present in New Zealand on the date of commencement of this Act" (ie, 29 July 1998). For the purposes of the HSNO legislation, genetic modification of a previously present species of a micro-organism produces a new organism.

Medicines covered by the exemption applying to human medicines are not exempt from the HSNO legislation when used as veterinary medicines.

Substances used in the manufacture of medicines in New Zealand by licensed medicine manufacturers are not exempt and importers and manufacturers must comply with the HSNO legislation.

The web site <http://www.hsno.govt.nz> is dedicated to the HSNO legislation and its application.

The web site <http://www.epa.govt.nz/> includes information on EPA procedures together with a [searchable register](#) of applications and approvals under the HSNO Act.

Where a sponsor wishes to distribute a new medicine that is a medical gas or new organism as defined above, the sponsor must apply separately to both Medsafe and EPA for consent using their respective application forms and procedures. Details of the date and status of the application to EPA must be provided in the New Medicine Application. The medicine concerned may not be distributed in New Zealand until consent from both agencies has been granted.

In the event of such an application to Medsafe and EPA, the two agencies will work together (subject to any confidentiality limitations imposed by the applicant), sharing relevant information and evaluation reports as appropriate, and co-ordinating their activities as far as is practical to ensure the efficient and effective administration of the requirements of the Medicines and HSNO legislation.

For further information about the HSNO and EPA requirements for obtaining consent to import and or release products controlled under the HSNO legislation, contact:

The Manager, Operations
Environmental Protection Agency New Zealand
Level 1, BP House
20 Customhouse Quay
PO Box 131
Wellington
Telephone: (04) 473 8426
Fax: (04) 473 8433
Web site: <http://www.epa.govt.nz/>

1.11.3. Standards and pharmacopoeia

Where a product is required to conform (or is claimed to conform) to any particular “standard” or pharmacopoeial monograph, it must comply with *all* of the requirements (including test methods, unless otherwise justified) of the *current version* of that standard or pharmacopoeial monograph. Where a pharmacopoeial monograph exists for an ingredient, this is considered to be the minimum requirements.

1.12. Consent not to be used for Promotional Purposes

Ministerial consent for the distribution of a new or changed medicine, or related product is not to be construed as an endorsement of any claim made for the product. No reference may be made to this consent in any label or advertising, promotional or other published material about the product.

1.13. Supplying Unapproved Medicines

An “unapproved medicine” is a medicine for which full or provisional consent for distribution has not been granted. A general exemption from the consent provisions for new and changed medicines is provided in [Section 29 of the Medicines Act](#), permitting the supply of any medicine (including an unapproved medicine) to a medical practitioner at his/her request, to treat a particular patient under his/her care. The supply must be initiated by the medical practitioner and the supplier may not advertise the availability of the medicine.

[Medsafe’s web site](#) lists unapproved medicines reported to Medsafe as being supplied in New Zealand, and includes further information about the responsibilities of the supplier and the medical practitioner and the rights of the patient involved in the supply of an unapproved medicine under the provisions of [Section 29](#).

The supplier (ie, the New Zealand importer or manufacturer) must have a licence issued under the Medicines Act 1981 which allows the supply of the medicine, or be exempt from this requirement under [Section 26](#), and must also maintain complete and accurate records of the information listed below. The records must be stored in a secure and confidential manner in the supplier’s New Zealand office and be available for audit by Medsafe if required. The information to be recorded and stored is:

- ☞ name(s) of the medical practitioner(s) who requested supply of the medicine
- ☞ name(s) of the patient(s) the medicine was required for
- ☞ dose form(s) and strength(s) of the medicine supplied
- ☞ date(s) on which the medicine was supplied
- ☞ name(s) of the place(s) the medicine was supplied to.

Suppliers of unapproved medicines must also notify the Manager Compliance Management, Medsafe, PO Box 5013, Wellington, as soon as practicable after the end of every month in which the medicine has been supplied, of the following:

- ☞ international non-proprietary name (INN) of the medicine
- ☞ trade name of the medicine
- ☞ pharmaceutical form
- ☞ month and year of supply

The form for reporting to Medsafe the supply of unapproved medicines is provided in [Part E, Section 1.6](#) of these guidelines.

1.14. Medical Advertisements

Superseded. Please refer to [Part 7](#) of the *Guideline on the Regulation of Therapeutic Products in New Zealand*.



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Part B:

What sort of application for approval is required?

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Section 1: Application Types

Section summary

1. To obtain Ministerial consent to distribute a new medicine or related product, the distributor must submit to Medsafe a “**New Medicine Application**” (NMA) or “**New Related Product Application**” (NRPA), together with supporting data.
2. When a material change to a previously approved medicine or related product is planned, the distributor or New Zealand manufacturer must notify the Director-General of Health of the change by submitting a “**Changed Medicine Notification**” (CMN) or “**Changed Related Product Notification**” (CRPN).

Legislation to read in conjunction with this section

Medicines Act 1981

Section 3: Meaning of ‘medicine’, ‘new medicine’, ‘prescription medicine’ and ‘restricted medicine’

Section 20: Restrictions on sale or supply of new medicines

Section 23: Minister may give provisional consent

Section 24: Distribution of changed medicine restricted

1.1. When is a Medicine a “New Medicine”?

The term “new medicine” is defined in [Section 3](#) of the Medicines Act. In practical terms, a new medicine is:

- ☞ a medicine for which Ministerial consent for distribution in New Zealand has not previously been granted, or
- ☞ an approved medicine that has undergone a material change that has resulted in its referral to the Minister under [Section 24](#)(5) of the Act, or
- ☞ a medicine that has previously been approved but has not been generally available in New Zealand during the five years immediately preceding the date on which it is proposed to become available.

A medicine is considered to have been “generally available” if, during the relevant five year period:

- ☞ the product has been sold or offered for sale in New Zealand on one or more occasions, or the product has been advertised in New Zealand as available for sale, or
- ☞ the regulatory file for the approved medicine has been updated through either a Changed Medicine Notification (CMN) or an application for a labelling exemption, or
- ☞ the product has been the subject of a submission made to [PHARMAC](#) for a tender.

1.1.1. Evidence that a medicine has been generally available

An applicant wishing to show that a product is not a new medicine because it has been “generally available” must support that claim by providing:

- € evidence of one or more sales during the relevant period (eg, invoice), or
- € evidence of importation (eg, customs clearance form), or
- € evidence of listing in a sales catalogue or price list from the relevant period, or
- € a statement identifying regulatory activity for the product, such as a CMN.

The claim must be supported by a declaration from a person in New Zealand that the evidence is genuine, and that any documents provided are true copies of the original documents. The original documents must be made available on request.

1.1.2. Previously approved medicine that has not been generally available

When a sponsor wishes to commence or re-commence distribution of a previously approved product that has not been generally available in New Zealand in the last five years a New Medicine Application must be submitted, otherwise, the medicine may only be supplied as an unapproved medicine under [Section 29](#) of the Medicines Act (see [Part A, Section 1.13](#) of these Guidelines for details). An appropriate application fee will be required based on the amount of evaluation and administrative work required, as determined by the Team Leader for the product area.

The data must include the elements described in [Section 21](#) of the Medicines Act. However, where the details are the same as those submitted in the original application for consent, or in any subsequent CMN, it will be sufficient to submit a declaration to that effect.

Where the details differ, the difference should be detailed and supporting data provided in the same way as is required for a CMN. If the change(s) is such that the safety profile of the product may have been altered, the data package should include a report of post-marketing surveillance from other countries in which the product has been marketed.

1.1.3. Combination packs of currently approved medicines

A new combination pack containing two or more currently approved medicines packaged together constitutes a new medicine and the Minister’s consent for its distribution must be obtained before it may be distributed. [Section 2](#) of the Medicines Act 1981 provides a definition of package.

1.2. What is a New Active Substance?

A chemical or biological active substance (also known as an active pharmaceutical ingredient, API) is a **New Active Substance**, in line with the European Union definition, when it is:

- ☞ a chemical, biological or biotechnological substance for which Ministerial consent for distribution as a medicine in New Zealand has not previously been granted, or
- ☞ an isomer, mixture of isomers, an ester, a complex or other derivative, or a salt, of a chemical substance with Ministerial consent for distribution as a medicine in New Zealand but differing in properties with regard to safety and efficacy, or
- ☞ a biological or biotechnological substance for which Ministerial consent for distribution as a medicine in New Zealand has been granted, but differing in molecular structure, nature of the source material or manufacturing process.

1.3. New Medicine Applications

A **New Medicine Application** (NMA) is an application under [Section 20](#) or [Section 23](#) of the Medicines Act seeking the Minister's consent to distribute a new medicine.

In practice, the power to approve medicines is delegated to a senior Ministry of Health officer, referred to as the Minister's delegate.

To facilitate administrative processing of applications, NMAs are divided into three types as detailed in the following Subsections 1.3.1 to 1.3.3.

1.3.1. New higher-risk medicine applications

A New Higher-risk Medicine Application (NMA-H) is an application for Ministerial consent to distribute a:

- ☞ new medicine containing a new active substance (ie, a new chemical, biological or biotechnological entity)
- ☞ new medicine with provisional consent under [Section 23](#) of the Medicines Act (the data requirements are different for these applications)
- ☞ medicine (with full Ministerial consent under [Section 20](#)) for which provisional consent for distribution under [Section 23](#) has previously been granted
- ☞ new fixed combination product containing a prescription medicine
- ☞ new medicine with a new route of administration or novel pharmaceutical form
- ☞ new inhaled prescription medicine which acts locally at the bronchial site
- ☞ prescription medicine with a new indication (see [Section 3](#) for further explanation)
- ☞ new vaccine
- ☞ new blood product
- ☞ new multi-source biological or biotechnological medicine.

1.3.2. New intermediate-risk medicine applications

A **New Intermediate-risk Medicine Application** (NMA-I) is an application for consent to distribute a new medicine that does not contain a new active substance and is a:

- ☞ multi-source prescription medicine. [Note that a multi-source biological or biotechnological medicine is a higher-risk medicine. The term “multi-source medicine” is now used in place of the term “generic medicine”.]
- ☞ Controlled Drug for which a prescription is required
- ☞ medicine with a new (but not novel) pharmaceutical form or a new strength or additional flavour of an approved prescription medicine
- ☞ prescription medicine with an extended indication (see [Section 3](#) for further explanation)
- ☞ injectable medicine
- ☞ irrigation solution
- ☞ dialysis solution
- ☞ medical gas.

1.3.3. New lower-risk medicine applications

A **New Lower-risk Medicine Application** (NMA-L) is an application for consent to distribute a new medicine that:

- ☞ is not defined above as a Higher-risk or Intermediate-risk Medicine, **and**
 - ☞ may be supplied without a prescription (ie, an OTC product), **and**
 - ☞ is recommended for indications that are already well documented for the active ingredient(s), **and**
 - ☞ is presented in a pharmaceutical form that is monographed in a pharmacopoeia, **and**
- either**
- ☞ contains active ingredients that are the subject of a pharmacopoeial monograph **or**
 - ☞ contains active ingredients that have a well documented history of use in OTC products (eg, as evidenced by entries in *Martindale* etc.) **or**
 - ☞ has active ingredients that are contained in one or more other products marketed OTC in New Zealand.

Lower-risk medicines may include products required to be sterile (eg, eye drops).

A product containing a Controlled Drug for which a prescription is not required (eg, pholcodine linctus or a codeine-containing combination analgesic) is evaluated using the New Lower-risk Medicine assessment procedure, provided it meets the criteria listed above.

New Intermediate- and Lower-risk Medicine Applications are sometimes referred to as “abridged” applications, because they do not contain the clinical and toxicological data required in a New Higher-risk Medicine Application. New Lower-risk Medicine Applications require less data as the medicine poses a lower-risk and can, therefore, safely be subjected to a lower level of regulatory control.

Each unique product is the subject of a separate product approval and has its own separate entry in Medsafe’s Therapeutic Products Database (SMARTI). A unique product is defined by its name, dose form, active ingredient(s), strength, flavour (if applicable) and classification. When an application is made for consent to distribute a new unique product, a New Medicine Application must be submitted. Reduced data requirements and evaluation fees apply to New Medicine Applications for products that are closely related to an existing approved product.

1.4. Referrals under Section 24(5) of the Medicines Act 1981

[Section 24](#) of the Medicines Act sets out restrictions on the distribution of changed medicines. Subsection 5 permits the Director-General of Health to refer a medicine (that is the subject of a CMN) to the Minister in certain circumstances. Such a referral occurs when a CMN is so large or complex that the changed product should not be allowed to be distributed until the changes have been fully evaluated. An example of such a change would be a major new indication. Once the CMN has been referred to the Minister under [Section 24](#) (5) of the Medicines Act, the application becomes an NMA. The timeframe for a CMN referred under Section 24 (5) of the Medicines Act is 200 calendar days from the date of referral, the same as a new prescription medicine.

1.5. Changed Medicine Notifications and Changed Related Product Notifications

A **Changed Medicine Notification (CMN)** or **Changed Related Product Notification (CRPN)** is a notification to the Director-General of Health by the sponsor of a product, under [Section 24](#) of the Medicines Act, of a planned material change to an approved product (this includes prescription and non-prescription medicines and related products), and the reasons for the change.

Where a medicine or related product is distributed as a complete finished product by one (primary) sponsor and the same finished product is also distributed by a second sponsor in a combination pack together with another product(s), both sponsors are responsible to ensure that the second sponsor is informed and the Director-General of Health is notified (via a CMN or [CRPN](#)) of any material changes affecting the medicine or related product in each of its presentations. There should be a commercial agreement between the two sponsors ensuring that the necessary information is exchanged between them and the necessary CMNs or CRPNs are lodged with Medsafe. The primary sponsor may lodge the appropriate CMNs or CRPNs for both presentations. A CMN or CRPN is required for each presentation of the product as a consent must be issued for each presentation.

If any change to a product results in a new active ingredient, new combination of active ingredients, new strength, new dose form, new flavour or new trade name an NMA or NRPA (**not a CMN or CRPN**) is required. The NMA or NRPA must be kept separate from and will be

processed separately from any other CMN or CRPN. The “new product” cannot legally be distributed until consent has been granted and published in the [New Zealand Gazette](#).

The timeframe for CMNs is usually 21 days if there are no questions from the evaluator. There is a 45 day legislative requirement for the initial evaluation of a CMN. Currently, there is no mechanism for priority assessments of CMNs..

1.5.1. Material changes to medicines and related products

A material change to a medicine or related product may require evaluation (in which case an evaluation fee is payable) or be self-assessable (in which case an administrative fee is payable). Assessable changes are notified through a CMN or CRPN and consent must be obtained before the change is made. Ask Medsafe for advice if there is doubt about whether a proposed change is notifiable or not.

Often one change in a product leads automatically to other changes (eg, a change in formulation will often result in changes in manufacture, quality control and stability). Details of the various types of assessable and self-assessable changes and the applicable fees are given in the CMN and CRPN forms (see [Part E, Section 1.3 – 1.5](#) of these Guidelines). The forms include common material changes (and changes consequent to these) and are designed to be as comprehensive as possible. If an intended change is not included in the relevant form, seek advice from Medsafe.

For a self-assessable change, there is no requirement to obtain consent prior to making the change. However, the notification must precede the change. The onus is on the applicant to ensure that data to support the change are held and could be made available on request. Such changes are to be notified using the same CMN or CRPN form as used for notifying assessable changes.

Medsafe carries out random audits of self-assessable changes and, where any significant problems are identified, the sponsor is required to rectify these. Where a CMN or CRPN rather than a SACN should have been submitted, the sponsor is asked to submit this.

1.6. Changing the Registration Situation

Sponsors who do not wish to maintain published data sheets for prescription and restricted medicines can designate their medicines “not available” in the therapeutic products database. Sponsors of other medicines can also choose to designate their products ‘not available’ if they wish to communicate the availability to the public and healthcare professionals.

Sponsors who wish to surrender consent because they do not intend marketing the medicine again in New Zealand may notify Medsafe and the status will be updated to ‘approval lapsed’. Approval lapsed is also used to denote medicines that have been not been generally available for more than five years as described in section 1.1.2.

A change in the registration status to ‘not available’ or ‘approval lapsed’ can be effected either by notification as part of a CMN/SACN or notified to Medsafe at any other time. Sponsors may choose to use the Product Status Change Request form. Sponsors should include advice as to when the product was last marketed in New Zealand.

To change the registration situation from 'not available' to 'consent given' or 'provisional consent', a CMN is required to be submitted and granted consent prior to the registration situation being updated and the product being reintroduced into the market. When requests are submitted as part of a CMN it should be clearly identified in the cover letter. For prescription or restricted medicines the CMN must include a revised data sheet to demonstrate that all required updates have been included. The CMN must undergo evaluation and self-assessable change notifications will not be accepted.

If a sponsor determines that a CMN is not required because the regulatory file has been kept up to date, a justification letter or Product Status Change Request form, for the registration situation to be changed to 'consent given' or 'provisional consent' should be provided to Medsafe. Medsafe will review the justification letter or form to ensure that all requests for CMNs have been addressed prior to the registration situation being updated and the product being reintroduced into the market.

CMNs, justification letters or Product Status Change Request Forms must be submitted at least 90 days prior to the intended date distribution will commence. Justification letters should be addressed to the Manager, Product Regulation.

If approval has lapsed, consent to the distribution of a new medicine needs to be granted before the product can be reintroduced onto the New Zealand market as described in section 1.1.2.



MEDSAFE

NEW ZEALAND MEDICINES
AND MEDICAL DEVICES
SAFETY AUTHORITY

A BUSINESS UNIT OF
THE MINISTRY OF HEALTH

New Zealand Regulatory Guidelines for Medicines

Part C: Requirements for application types

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Section 1: Clinical Trials of Medicines

Superseded. Please refer to [Part 11](#) of the *Guideline on the Regulation of Therapeutic Products in New Zealand*.

Section 2: New Medicine Applications

Section Summary

This section outlines the format and data requirements for applications for Ministerial consent to distribute new and changed medicines and related products.

Legislation to read in conjunction with this section:

[Medicines Act 1981](#)

[Section 21:](#) Applications for Minister's consent

[Section 23:](#) Minister may give provisional consent

[Section 24:](#) Distribution of changed medicines restricted

2.1. Formats for New Medicine Applications

A new medicine application (NMA) is to be presented in two sections, ie, the administrative information and the dossier of supporting data to establish the quality, safety and efficacy of the product.

The **administrative data** consists of the following documents (as applicable for the particular type of product):

Covering letter

Completed NMA form(s) (<http://www.medsafe.govt.nz/regulatory/forms.asp>)

EDQM Certificates of Suitability (See [Part D, Section 6.2](#))

Good Manufacturing Practice (GMP) documentation (see [Part D, Section 5](#))

Labelling (see [Part 5: Labelling of Medicines and Related Products](#))

Information leaflet/Package insert/CMI (See [Part 5: Labelling of Medicines and Related Products](#))

Data sheet (see [Part 10: Requirements for Information for Prescribers and Consumers](#))

Copies of overseas evaluation report(s) and approval documentation.

An NMA form must be completed for all new medicine applications. A separate form should be completed for each separate medicine (name, dose form, drug substance, strength, classification and flavour as applicable).

The accompanying **dossier of supporting quality, safety and efficacy data** includes the following (as applicable for the type of application):

Overview and Summaries of the data

Chemical, Pharmaceutical and Biological quality documentation (including separate Drug or Plasma Master File(s))

Pre-clinical/Toxicology documentation

Clinical documentation

Bioavailability or bioequivalence data

The preferred format for the dossier of supporting data for NMAs and new related product applications (NRPAs) is the ICH Common Technical Document (CTD). The dossier should be comprised of Modules 2 (Overviews and Summaries of the Quality, Non-clinical and Clinical data), 3 (Quality), 4 (Non-clinical Study Reports) and 5 (Clinical Study Reports) as detailed in the ICH Guideline “Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use”

(http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R3_Organisation/M4_R3_organisation.pdf).

In exceptional circumstances Medsafe also accepts the EU format for the dossier as detailed in the European Commission’s Rules Governing Medicinal Products in the European Union, Volume 2B: Notice to Applicants, 1998 edition, in cases where the dossier has previously been assembled and submitted in that format to a regulatory authority in Europe or Australia.

Medsafe does not expect applicants to re-format such material to the CTD format. If an application dossier in EU format is available, this should be submitted unchanged **except** for “Part IA” (Administrative Data) which must be replaced with the New Zealand NMA form so that all information relevant to the New Zealand application is presented and that specific to EU administrative requirements is omitted. The accompanying “Part IB” documents (GMP documentation, data sheet, labelling, etc) should be submitted as they are or adapted to New Zealand requirements, as appropriate.

Where an application dossier in either CTD or “EU” format is not available, Module 1 should be submitted according to the New Zealand format and requirements and the remainder of the data package supporting the NMA should be assembled as far as reasonably possible to coincide with the CTD Modules 2 – 5.

A detailed Table of Contents must be provided with any dossier, regardless of the format, to assist evaluators in their assessment.

2.2. Data Requirements for Electronic Submissions

2.2.1. Higher-Risk Application Requirements

All High-risk NMAs are required to be submitted with two copies of an electronic dossier. This is to allow the clinical and pharmaceutical chemistry evaluators to simultaneously evaluate the application.

2.2.2. Lower-Risk Application Requirements

Inclusion of two copies of an electronic dossier has been mandatory for all OTC medicine submissions from 1 September 2013. This requirement is outlined in the staged implementation of the OTC reforms process and is required to support the future introduction of a single entry portal for lodgement of applications.

2.2.3. All Other Applications

Applicants are encouraged to submit two copies of an electronic dossier, in addition to one hard copy of the dossier, for all intermediate-risk NMAs. Applicants should also consider electronic dossiers for CMNs that contain substantial supporting data.

2.2.4. Submission Process

One hard copy of modules 1 to 5, including a complete table of contents for each module, is typically required. However, modules 4 and 5 can be submitted solely in electronic format if they contain a large number of volumes.

A hard copy of the contents pages to modules 4 and 5 must be provided when submitting these modules solely in electronic format.

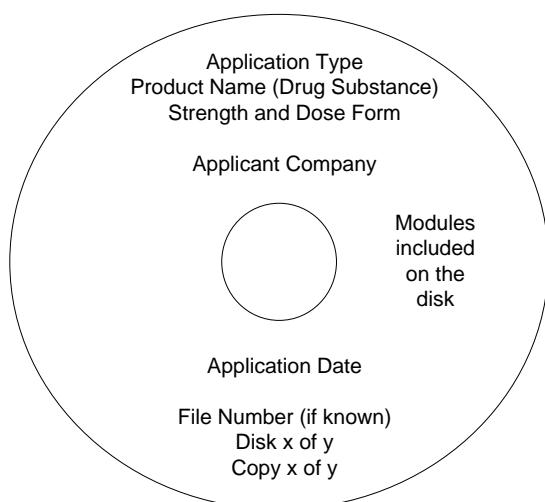
Overseas evaluation reports, and associated correspondence, submitted as part of the abbreviated evaluation process must be provided in hard copy.

Two copies of the electronic dossier should be provided on CD or DVD in the required format (see below). Medsafe cannot accept electronic dossiers on a data stick, hard drive, rewritable disk or similar media. Before accepting the electronic dossier, it will be checked for compatibility with Medsafe systems. A replacement copy may be requested at any point during the duration of consent.

The physical disks should be clearly labelled with the following:

- application type
- product name (drug substance)
- strength and dose form
- applicant company
- application date
- file number (if known)
- disk and copy number
- modules included on the disk.

A suggested format is graphically represented below.



If a sticker is used to label the disk it must not impact on the ability for the disk to be read. An additional label is not required on the CD or DVD case.

Electronic dossiers should be packaged carefully and securely to ensure they arrive in a usable condition. In Medsafe's experience a courier bag by itself does not provide adequate protection for shipping. If the electronic dossier is being provided separately from the hard copy it should be sent in a secure package with an accompanying letter; loose disks are not appropriate.

Applicants submitting electronic dossiers must provide an assurance that the content of the electronic copies is identical to that of the paper. As with all applications submitted to Medsafe, applicants must also commit to holding a complete hard copy of the data set for the duration of consent and for a period not less than five years from the date approval lapses. The complete data set may be requested at any time.

2.2.5. Formatting of Electronic Submissions

Medsafe does not require dossiers to be prepared with eCTD software or in NeeS format, but electronic format should:

- be in PDF except the application form which may be in MS Word
- have files and folders structured to correspond with CTD format
- be readable in Acrobat Reader version X (10)
- enable the user to easily view a clear and legible copy of the information
- enable the user to print each document page by page maintaining fonts, orientation, formats and page numbers
- include a well-structured table of contents with hyperlinks to sections
- allow information (including images) to be copied and pasted into other common programmes
- contain hyperlinks and bookmarks to cross-reference information
- virus checked using up to date programmes (with confirmation of this to be provided in the cover letter)
- not have any security settings or password protection enabled.

Organisation of any electronic response to a request for information (RFI) should follow the same principles as the initial electronic submission. However, responses can be aligned with the

questions (as currently occurs in hard copy responses) rather than be structured to correspond with CTD format.

2.2.6. Source of Electronic Document

It is preferable that dossiers are created from an electronic source document so they can be searched and copied to other documents.

Scanned paper documents are inferior to those produced from an electronic source document as they are more difficult to read and do not allow search function capability. If scanning is essential then optical character recognition software (OCR) is required and text verified as accurate prior to submission. Scanning must be at resolutions to ensure the document is legible on screen and when printed. As a guide, text documents should be scanned at 300 dpi and photographs at 600 dpi.

The following documents do not need to be converted to searchable text:

- GMP certificates
- Certificates of Analysis
- Manufacturer's licences
- Certificates of Suitability
- Documents in foreign languages and for which a translation is provided as searchable text
- Literature references (except those in bibliographic applications)
- Hand-written documents such as batch records and operating logs.

This guidance is based on *Providing Regulatory Submissions in Electronic Format - General Considerations* issued by the US Food and Drug Administration.

For complete details refer to the [FDA guidance](#).

2.3. Data Requirements for New Medicine Applications

The requirements for the data supporting a new medicine application depend upon the category of product involved:

New Higher-risk Medicine (NMA-H)

New Intermediate-risk Medicine (NMA-I)

New Lower-risk Medicine (NMA-L)

An application for provisional consent to distribute a new medicine

Please note that a non-prescription medicine does not automatically fall into the lower-risk medicine category.

New intermediate-risk and lower-risk medicines usually contain active ingredients that are listed in a pharmacopoeia and claim indications for which there is sufficient supportive published literature. Where this is not the case, a new intermediate-risk or new lower-risk medicine

application may need to contain clinical documentation to support the proposed indications, and also possibly relevant toxicological and pharmacological documentation.

While an application for provisional consent need not contain the same detail of safety and efficacy data as that required for full consent, all available information should be included, along with an explanation of the type of data still being collected and when these data will be available.

When the product that is the subject of an NMA is closely related to an existing product, such as a new strength, the applicant is only required to submit data relevant to the introduction of the new product. The application must specify all differences between the new and existing products and provide data to support the safety, quality and efficacy of the new product. A complete dossier duplicating data already supplied for an existing product is not required.

Different pharmaceutical forms and strengths or flavours of a medicine require separate application forms, but may be supported by reference to the same dossier of information.

Where a medicine has been evaluated and approved in Australia, Europe, Canada or the USA, and the overseas approval documentation and evaluation reports are available, sponsors should provide copies of those reports along with an indication as to whether the supporting data submitted overseas was identical or not to the data submitted with the New Zealand application.

Product Development Pharmaceutics are not normally required for lower-risk medicines. They may be required for unusual dose forms or formulations.

Where pharmacopoeial test methods are used to control a finished product, sufficient validation data should be provided to confirm that the test methods work satisfactorily for the product concerned.

Applications to distribute medicines described as biosimilars need to be accompanied by data according to annexes to the CHMP Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Applications must also include any additional data as required by the Medicines Act 1981 and the NZRGM and a risk management plan covering the introduction of the product to New Zealand. Further information about Medsafe's position on biosimilars is available on its website at <http://www.medsafe.govt.nz/profs/RIss/Biosimilars.asp>

2.4. Standard Requirements for New Multi-source (Generic) Prescription Medicines

Medsafe's standard requirements for the data for new intermediate-risk medicines are as set out below. Dossiers are assessed for conformity with these requirements.

2.4.1. Administrative Information

The proposed proprietary name for the product must be clear, unambiguous, not unacceptably similar to, or likely to be confused in any way in print, handwriting or speech with, another

medicine currently registered in New Zealand, and not misleading in any way with regard to the nature, composition, purpose, uses or effects of the product.

Good Manufacturing Practice (GMP) certification or other evidence of GMP compliance must be provided for each finished product manufacturing, testing and packing site and the certification: (a) relates to the product (or product class) concerned, (b) must be issued by authorities recognised by Medsafe, and (c) will not have expired or be more than 5 years old by the time the product is likely to be approved for distribution in New Zealand.

Appropriate evidence of GMP (in the form of a GMP certificate) must be provided (or have been provided previously) for each active ingredient manufacturing site.

The labelling must comply with the New Zealand Medicines Regulations and Guidelines (see [Part 5: Labelling of Medicines and Related Products](#)) or a labelling exemption may be requested according to the criteria set out in [Part 5, Section 2.3](#).

If applicable, the labels must allow easy discrimination between the different strengths of the product.

The draft data sheet must comply with the NZ Medicines Regulations and Guidelines (see [Part 10: Requirements for Information for Prescribers and Consumers](#)).

In the case of a multi-source medicine, the data sheet must be consistent with that of the corresponding innovator product.

If applicable, any package insert/information leaflet supplied with the product must be consistent with the New Zealand product details and the data sheet.

If any excipients in the product are unsuitable for particular patient populations, appropriate information or warnings must be included on the label (or, when space on the label does not permit, in an information leaflet/package insert) and also in the data sheet.

2.4.2. Chemical, Pharmaceutical and Biological Documentation

Composition

The dose form and formulation must be adequately justified and be appropriate for the medicine concerned. All of the ingredients must be acceptable for use in human medicines and be compatible with each other. Dose delivery must be consistent within clinically acceptable limits.

If relevant, any antioxidants and any chemical or anti-microbial preservatives included in the product must be adequately justified and their effectiveness must be established.

Adequate measures must be taken to ensure that any animal-derived ingredients (eg, gelatin, magnesium or calcium stearate, stearic acid) used in the product are free from TSE contamination.

Different strengths of the product must be readily distinguished (eg, by differences in size, colour, shape, markings, etc).

If tablets are scored, evidence that the tablets split evenly must be provided. If a tablet is not intended to be divided, or has not proven to be capable of providing a divided dose, then the "Presentation" and "Dosage and Administration" sections of the tablet's data sheet should contain the following statement: "Do not halve tablet".

The primary (immediate) and secondary (outer) packaging and packaging materials, closures, induction or tamper-proof seals, pack sizes, any dosing device, and any desiccant or cotton wool contained in the package must be appropriate for the product.

If the New Zealand Medicines Regulations require the product to be in a safety container, it must be so packaged. The current legislative definition of safety packaging in New Zealand is blister strip packaging. (Regulation 2 of the Medicines Regulations 1984)¹ In addition, Medsafe requires all anti-depressants, marketed as a solid oral dose form, to be contained within safety packaging.

Manufacture of Active Ingredient(s)

Unless previously submitted and approved, a satisfactory Drug Master File(s) or equivalent information about the manufacture of the active ingredient(s) from each supplier of bulk active ingredient must be submitted.

The DMF must describe in detail: the “route of synthesis”, each step in the manufacturing and purification process, the reaction conditions and in process controls for each step, the quality control of starting materials, reagents, catalysts, solvents and any isolated intermediates, as well as any subsequent processing (eg, milling) of the bulk substance.

The DMF must also provide proof of chemical and stereochemical structure of the substance (and of any significant impurities) using appropriate physical, chemical and spectroscopic methods.

Where relevant, adequate evidence of the crystalline form produced and control thereof must be provided.

Manufacture of Finished Product

The manufacturing, sterilisation (if any) and packaging processes, the equipment used, and batch sizes must be described in detail, appropriate and justified.

Any overages or ranges of quantities for the active ingredient(s) or any excipients must be appropriate and adequately justified.

If relevant, any sterilisation processes must be justified, and it must be established that harmful by-products are not formed during the sterilisation process.

Any overfill of the container(s) must be justified.

Any solvents or gases used in the manufacturing process must be of adequate quality.

If alternative processes are intended at some steps in the manufacture, these have been justified and shown to yield finished product of equivalent quality.

The in-process controls (including temperatures, mixing times and speeds, filter integrity), test methods and acceptance limits at each step in the manufacturing, sterilisation (if any) and

¹ Update to Section 8.3: Standard requirements for new multi-source (generic) prescription medicines (Sept 2003)

packaging processes must be defined, appropriate and adequate to assure batch quality and unit-to-unit consistency.

If relevant, any processing (eg, neutralising, cleaning, washing, sterilisation) of the containers before filling must be adequately controlled.

If relevant, controls on sterility of the equipment, product and containers must be adequate throughout the process.

If sterilisation is by filtration, the bioburden of the product before filtration must be adequately controlled, the filter membrane pore size must be not more than 0.22 microns, and the integrity of the filter must be checked before and after use.

If sterilisation is by autoclaving or gamma irradiation, the equipment and procedures must be described in detail and adequately controlled.

If sterilisation of the product or container is by treatment with ethylene oxide, its use must be the only viable option and the residue level must be controlled to not more than 1 ppm in the product or 1 mcg/ml container volume, and any chlorohydrin residue must be controlled to not more than 50 ppm in the product or 50 mcg/ml container volume.

All critical steps in the manufacturing process (including any cleaning and/or sterilisation steps) must have been adequately developed and validated at each manufacturing site at either production scale or at pilot scale ($\geq 10\%$ of full scale or 100,000 solid dose units, whichever is the greater unless otherwise justified) using production scale equipment.

If only pilot scale validation has been completed, confirmation that full scale validation is scheduled for when commercial scale production commences must be provided.

Quality Control of Active Ingredient(s)

(a) Controls applied by manufacturer of bulk active ingredient

Unless previously submitted and approved, a satisfactory Drug Master File (DMF) or a Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP) issued by the European Directorate for the Quality of Medicines (EDQM), must be submitted from each supplier of bulk active ingredient.

The active ingredient specifications applied by the manufacturer of the bulk active ingredient must be in accordance with a recognised pharmacopoeia (eg, Ph Eur, BP, USP) or, if non-pharmacopoeial specifications are applied, these must cover all of the relevant identity, organoleptic, physical (including crystalline form and particle size distribution, if applicable), chemical, stereochemical and microbiological quality parameters.

Justification must be given for the selection of any non-pharmacopoeial tests, test procedures, requirements and limits.

If certain tests are not carried out routinely, adequate justification must be provided.

Physical, chemical and microbiological test procedures (whether pharmacopoeial or not) must be self-validating or have been validated in accordance with pharmacopoeial standards or ICH guidelines.

All assay and related product/degradation product and residual solvent impurity level tests must have been validated (as appropriate) for specificity/selectivity, limit of detection, limit of quantitation, accuracy, precision, repeatability, linearity, stability of solutions, and robustness/ruggedness.

Proof must be provided that the related substance assay procedure is adequate to detect and control all of the related substance impurities actually or potentially present in the bulk substance produced using the intended manufacturing process.

Satisfactory representative batch analytical data must be supplied for typical batches of bulk active substance.

Any Certificates of Analysis submitted must have been signed.

If a "house" reference standard is used in the assays, characterisation and analytical data confirming its suitability for use must be provided.

(b) Controls applied by manufacturer of finished product

The active ingredient specifications applied by the finished product manufacturer in testing bulk active substance before use in manufacture of the finished product must be in accordance with a recognised pharmacopoeia (eg, Ph Eur, BP, USP) or, if non-pharmacopoeial specifications are applied, these must cover all of the relevant identity, organoleptic, physical (including particle size distribution, if applicable), chemical, stereochemical and microbiological quality parameters.

Justification must be given for the selection of any non-pharmacopoeial tests, test procedures, requirements and limits.

If certain tests are not carried out routinely, adequate justification must be provided.

Physical, chemical and microbiological test procedures (whether pharmacopoeial or not) must be self-validating or have been validated in accordance with pharmacopoeial standards or ICH guidelines in the testing laboratory(ies) used by the finished product manufacturer for routine quality control of the bulk active(s).

All assay and related product/degradation product and residual solvent impurity level tests must have been validated (as appropriate) for specificity/selectivity, limit of detection, limit of quantitation, accuracy, precision, repeatability, linearity, stability of solutions, and robustness/ruggedness.

Satisfactory representative batch analytical data generated by the finished product manufacturer(s) must have been supplied for typical batches of bulk active substance from each supplier.

Any certificates of analysis submitted must have been signed.

If a "house" reference standard is used in the assays, characterisation and analytical data confirming its suitability for use must be provided.

Quality Control of Excipient(s)

The identity and quality of all excipients (including capsule shells and their constituents, and any gases used in filling vials or ampoules) must be controlled by either pharmacopoeial or appropriate in house specifications.

Any non-pharmacopoeial specifications must be appropriate and adequately control identity, and physical, chemical and microbiological quality of the material.

Adequate measures must be taken to ensure that any ingredients of animal origin (eg, gelatin, magnesium or calcium stearate, stearic acid) used in the product are free from TSE contamination in accordance with EC and US guidelines.

Satisfactory representative batch analytical data must be provided for any excipients controlled by non-pharmacopoeial specifications.

Any certificates of analysis submitted must have been signed.

Quality Control of Packaging Materials (Immediate Packaging)

The packaging materials used (polymers, types of glass, etc.), containers, seals, closures and any delivery device(s) supplied with the product must be clearly defined, suitable for pharmaceutical use, and adequately controlled for identity, dimensions, physical and chemical properties, manufacturing defects, and sterility, as applicable.

Any plastic or rubber packaging/closure materials in contact with the product must be free from any leachable toxic impurities and must comply with Ph Eur and USP requirements for polymeric materials used in packaging of medicines.

Satisfactory representative batch analytical data must be provided for any primary packaging materials, containers and closures in contact with the product.

Any certificates of analysis submitted must have been signed.

Quality Control of Delivery Device(s)

Any delivery device(s) supplied with the product must be clearly defined, suitable for pharmaceutical use and adequately controlled for identity, dimensions, physical and chemical properties, manufacturing defects, sterility, and dose delivery, as applicable.

Quality Control of Intermediate Products

If there is an intermediate product, it must be controlled by separate, appropriate specifications that adequately control all relevant parameters.

Satisfactory representative batch analytical data must be provided.

Any certificates of analysis submitted must have been signed.

Quality Control of the Finished Product

The complete identity and quality of the finished product must be adequately controlled at release and throughout its shelf-life by appropriate pharmacopoeial or in house specifications that cover all of the necessary organoleptic, physical, dissolution, chemical, microbiological and dose delivery parameters relevant to the dose form.

It must be clear which requirements apply at release and which apply throughout the shelf-life.

If applicable, any non-pharmacopoeial test procedures used as replacements for, or in addition to, the procedures in a pharmacopoeial monograph must be appropriate and have been justified.

If all specified tests are not carried out routinely, justification must be provided.

The test procedures used must be self-validating or have been adequately validated in accordance with pharmacopoeial requirements or ICH guidelines at each of the testing sites intended for routine quality control of the product.

All assay and related product/degradation product and residual solvent impurity level tests must have been validated (as appropriate) at each testing laboratory involved in the quality control of the product for specificity/selectivity, limit of detection, limit of quantitation, accuracy, precision, linearity, repeatability, stability of solutions, and robustness/ ruggedness.

Satisfactory recent analytical reports must be provided for the final market formulation(s) of the product manufactured at least at pilot scale at each of the proposed manufacturing sites. Results must be included for each specified test and all of the reported test results must comply with the specifications. If not, an adequate explanation or justification must be provided.

Any certificates of analysis submitted must have been signed.

Stability of the Active Ingredient(s)

The stability of the active ingredient(s) is normally described in the associated DMF(s).

The stability data submitted must have been produced in accordance with ICH guidelines and adequately establish that the bulk active substance packaged in the intended storage container and stored under the prescribed storage conditions will remain within specifications for the whole of the claimed shelf-life or retest period.

Stability of the Finished product

The stability of the market formulations of the finished product (or formulations that may reasonably be expected to have the same stability) packaged as intended for marketing must have been tested in accordance with ICH guidelines (including the ICH requirements for the number and sizes of batches used) unless otherwise justified.

Preferably, more than one batch of active substance should have been used in the manufacture of the stability batches.

The stability trial protocol, packaging, packaging orientation (if relevant), storage conditions and test procedures must be described in detail.

All of the stability-indicating organoleptic, physical, chemical and microbiological quality parameters relevant to the dose form and type of packaging must have been included in the testing schedule and have been monitored using appropriate, clearly defined, validated (in the testing laboratory used for the stability samples), stability-indicating test procedures.

Any changes in test procedures during the stability trials must be justified and results correlated.

At least 12 months data for storage under the recommended storage conditions must be available and be submitted with the application (unless otherwise justified).

The stability data should be updated before submission.

Wherever relevant, results should be expressed quantitatively rather than as “complies” or “passes test”.

Any lack of mass balance between assays and degradation products must be explained or discussed.

If relevant, preservative levels or effectiveness must be monitored.

The results (and allowing for extrapolation within reasonable limits) must adequately support the proposed shelf-life under the recommended storage conditions (otherwise a shorter shelf-life may be granted until adequate stability data can be provided to support the proposed shelf-life).

If relevant, the stability of the product after first opening, reconstitution or dilution (as applicable) must have been investigated and shown to be adequate for the intended use of the product.

If relevant, adequate storage instructions and time-limits for use of the product after first opening or reconstitution or dilution must be stated on the draft product label, in any package insert, and in the data sheet.

Bioequivalence

If applicable, the bioequivalence (or, if more appropriate, clinical equivalence) of the product and that of the appropriate reference product marketed in New Zealand (or an acceptable alternative product) must have been established in accordance with the detailed requirements set out in Part D, [Section 2](#), [Section 7](#) and [Section 8](#).

The batches of trial and reference medicine used in the study must have been of acceptable quality.

The batch(es) of trial medicine(s) used in the biostudy must have been of adequate scale and truly representative of the product intended for marketing with respect to: (a) formulation, (b) crystalline form/polymorph of active ingredient, and (c) particle size distribution of the active (especially if <1% soluble in water) (or any differences in any of these parameters must be unlikely to affect the product’s bioavailability).

If the batch of reference product used in the study was obtained from outside New Zealand, adequate evidence that its formulation was the same as that distributed in New Zealand must be provided.

The results (eg, for T_{max}, C_{max} and mean plasma/serum concentrations after dosage) obtained in the biostudy must be consistent with the published pharmacokinetic properties of the medicine.

The pharmacokinetic data must have been subjected to the correct statistical analyses as detailed in [Part D, Section 7.10](#).

2.5. Abbreviated Evaluation Process

2.5.1. Introduction

The basis for the abbreviated evaluation procedure is the review of regulatory evaluation reports rather than a review of the medicine dossier. Therefore, the quality and availability of evaluation reports should be a fundamental consideration for applicants wishing to use the abbreviated evaluation process. This is particularly important if the product details sought for registration rely upon an overseas evaluation report for a variation in product details.

The abbreviated evaluation process is intended to be a simpler and quicker process than the standard evaluation process. This is reflected in the application fee.

The abbreviated evaluation process is not intended to be applicable to all medicine applications. For instance, it is known that the United States Food and Drug Administration (FDA) does not issue evaluations reports for generic medicine applications. Consequently, it is not possible to submit a generic medicine application through the abbreviated evaluation route if it is based upon FDA approval.

Medsafe reserves the right to re-route abbreviated evaluation applications to the standard evaluation process if the application does not fulfil the intent of this process.

The abbreviated evaluation process is not applicable to new lower-risk new medicine applications or Changed Medicine Notifications (CMNs). However, Medsafe strongly encourages applicants to consider providing international regulator evaluation reports and evidence of approval if this is available at the time of submission.

2.5.2. Application and evaluation process

Applicants seeking consent to distribute new higher-risk or intermediate-risk medicines have two options.

Standard evaluation process – by submitting a full dataset for assessment as required by the Medicines Act 1981 and the New Zealand Regulatory Guidelines for Medicines (NZRGM).

Abbreviated evaluation assessment – by submitting a full dataset for assessment as required by the Medicines Act 1981 and the NZRGM, as well as the additional information specified in Section 2.5.4 below.

For applications made through the standard evaluation process Medsafe will undertake a full assessment of the data provided. For applications made through the abbreviated assessment Medsafe will base its evaluation on the provided evaluation reports.

During the abbreviated evaluation process Medsafe will ascertain the following.

- Whether the submitted international regulatory evaluation reports are of a sufficient standard to allow an abbreviated assessment to occur.

If the evaluation reports are not of a desired standard the application will not be accepted. The applicant will be able to choose to resubmit the application to the standard evaluation process. Whether any product details are not supported by evaluation reports and approval documents.

If the differences are not trivial the applicant will be contacted and asked to either change the relevant aspect of their application; or resubmit the application to the standard evaluation process (additional fees will be required).

- Whether any aspect of the product poses any safety issues if used in the New Zealand market, and will determine whether the product requires evaluation against any Medsafe specific evaluation requirements.

Once evaluation has commenced, the applicant will **not be able to change** which pathway is used, nor will they be permitted to submit additional data for an application using the abbreviated process unless it is in response to a question from Medsafe.

2.5.3. Recognised regulatory authorities

For the purposes of the abbreviated evaluation process, Medsafe recognises the following regulatory authorities:

Australian Therapeutic Goods Administration (TGA)

United States Food and Drug Administration (FDA)

Health Products and Food Branch of Health Canada

Medicines and Healthcare products Regulatory Agency (MHRA)

European Medicines Agency (centralised procedure only)

EU member states (decentralised or mutual recognition procedure only).

2.5.4. Eligibility criteria

To be eligible for the abbreviated evaluation process the medicine must:

- be an an Intermediate-risk or High-risk medicine that has been approved by a recognised regulatory authority since 1 January 2001
- not be subject to any regulatory action that may result in a suspension or revocation of the market authorisation by any recognised regulatory authority
- have the same formulation as the product originally approved by the recognised regulatory authority
- have the same dosage and indications as the product originally approved by the recognised regulatory authority (does not apply to generic medicines)
- have current market authorisation issued by the recognised regulatory authority
- have undergone NO MORE THAN TWO of any of the following types of significant change and those changes must have been approved by the recognised regulatory authority:
 - significant changes in method of manufacture considered as a "Finished product manufacturing process – Grade 2" Changed Medicine Notification
 - addition of a new finished product testing site

- addition of a new finished product manufacturing site
- addition of a new active ingredient manufacturing site for which a Drug Master File is required
- addition of a new primary packing site
- extension of shelf-life (multiple extensions will be considered as one change as subsequent changes supersede earlier ones).

The application must be supported by a complete dataset as required by the Medicines Act 1981 and the NZRGM, consisting of Modules 2, 3, 4, and 5 (as applicable). The dataset should reflect the product details being sought for registration

The original dossier submitted to the overseas authority must be in Common Technical Document (CTD) format and the dossier (submitted to Medsafe) must have been updated to incorporate the supporting data for any changes approved by the recognised authority.

The overseas evaluation report(s) must correspond to CTD structure and must be a complete record of the assessment (redacted reports are not acceptable).

Evidence of approval by the recognised overseas authority of the medicine and any of the above significant changes to it, is included in the application to Medsafe. Such evidence in relation to applications from Europe can be in the form of either a marketing authorisation or notification from the authority of either a closed Centralised Procedure, Mutual Recognition Procedure, or Decentralised Procedure.

Note that a significant change that includes consequential changes can be counted as one change, providing that all changes were assessed and approved by the overseas authority at the same time as one application (eg, a new finished product manufacturing site is consequentially registered as a finished product testing and primary packing site – all is considered one significant change).

Medsafe still reserves the right to re-route any application to the standard evaluation process if the application does not fulfill the intent of the abbreviated evaluation process.

2.5.5. Required documentation

Applicants submitting applications for new medicines that meet the eligibility criteria will need to provide documentation describing the product and the history of the product's evaluation and approval by the recognised regulatory authority.

The following information must be submitted.

1. A covering letter requesting that the application be evaluated using the abbreviated process.
2. A complete Module 1 completed specifically for New Zealand registration.

Applicants should use the NMA form posted on the Medsafe website

3. A table of contents for the dossier to provide easy reference to the submitted information.
4. A table which sets out the events in the regulatory history of the product occurring from the date of the application for consent lodged with the recognised overseas regulatory authority through to the date of the application for consent to distribute in New Zealand. This table will need to include information under at least the following headings.

- a. Date of the event.
 - b. Event description (eg, type of application, request for further information).
 - c. Brief description, in chronological order, of correspondence with the recognised regulatory authority (with dates, name and designation of author and summary of content).
5. A copy of the approval letter and approved product details, including any attachments from the recognised regulatory authorities.
 6. A copy of the evaluation reports from a recognised regulatory authority that has approved the product.
 7. A copy of requests for information issued by the recognised regulatory authority that has approved the product and the responses to such requests.
 8. Evidence, if required, of the relevance of the submitted biostudy reference product to the New Zealand market reference product in line with the NZRGM.
 9. If applicable, details of the reason for and outcome of, any referral to arbitration by the Coordination Group for Mutual Recognition and Decentralised procedures (CMD(h)).
 10. Finalised labelling and packaging copy from the recognised regulatory authority and proposed New Zealand labelling and packaging².
 11. A copy of the drug substance specifications applied by the drug product manufacturer and approved by the regulatory authority.
 12. A copy of the drug product release and expiry specifications approved by the regulatory authority.

2.5.6. Fees

The fee schedule can be accessed at <http://www.medsafe.govt.nz/regulatory/fees.asp>

2.6. Provisional Consent

2.6.1. Introduction

Provisional consent, under section 23 of the Medicines Act 1981, may be granted when it is desirable that the medicine be sold, supplied, or used on a restricted basis for the treatment of a limited number of patients. Provisional consent is only granted for a period not exceeding two years and will then expire.

Conditions may be included with a medicine that has provisional consent. These may relate to the person whom the medicine may be sold or supplied, the area in which the medicine may be

² The product must comply with Medsafe's current labelling requirements.

distributed or other conditions. Any conditions relating to restrictions on supplying or prescribing the medicine are included in the *Gazette* notice.

2.6.2. Renewal of provisional consent

It is the sponsors' responsibility to ensure that provisional consent does not expire for the medicine. Applications for renewal of provisional consent must be submitted at least three months prior to the expiry of provisional consent. This is necessary to allow sufficient time for administrative processing, evaluation and publication of the *Gazette* notice. If an application is received less than three months before the expiry of provisional consent there may be insufficient time to process a renewal of provisional consent and it will be required to be treated as a new provisional consent.

Renewal of provisional consent is for a period of up to two years from the date of expiry ie, the current provisional consent expires on 30 October 2013 and the renewal of provisional consent is published on 22 August 2013, therefore provisional consent will now expire on 30 October 2015.

2.6.3. Conversion from provisional consent to full consent

Sponsors of medicines with provisional consent should address the data deficiencies that were identified during the initial application to convert to full consent under section 20 of the Medicines Act 1981. It is expected that a sponsor should generally submit an application for full consent within five years of provisional consent initially being granted.

If a medicine has any conditions relating to restrictions on supplying or prescribing then medicine it is not considered suitable for full consent at this time.

Provisional consent must be maintained during the period that the application is undergoing evaluation for full consent. The evaluation timeframes will not be adjusted to avoid renewal of provisional consent being required.

2.6.4. Fees

The fee schedule can be accessed at <http://www.medsafe.govt.nz/regulatory/fees.asp>

2.7. Abbreviated Process for Granting Provisional Consent

On 16 March 2009 Medsafe implemented a business rule to enable two categories of medicines that were supplied under section 26 and section 29 of the Medicines Act 1981 and used routinely in New Zealand hospital practice to be considered for approval under section 23 of the Medicines Act (provisional consent).

The business rule allowed applicants to provide evidence of routine use in hospitals *in lieu* of some of the typical safety, quality and efficacy data.

Since its inception Medsafe has received very few applications and has concluded that the medicines the scheme was intended to capture have either been approved or are no longer routinely used.

As a consequence this route to approval has been discontinued.

Applicants may still submit applications for provisional consent via the abbreviated route as described in section 2.5.

2.8. Priority Assessment of New Medicine Applications

2.8.1. Criteria for priority assessment

There are three eligibility criteria for granting priority assessment to a new medicine application. The criteria relate to medicines which address a significant clinical need, medicines which could deliver significant cost savings to the taxpayer, and medicines that are manufactured in New Zealand for export. The criteria are discussed below. Note that Changed Medicine Notifications are not eligible for priority assessment. Changed Medicine Notifications referred under Section 24(5) of the Medicines Act 1981 are susceptible to the same eligibility criteria for priority assessments as NMAs.

(A) Significant clinical need

Requests for priority assessment on the basis of significant clinical need will be considered for applications for products containing new active substances or where alternative products are not available. Vaccines for the prevention of diseases are treated in the same way as other agents for the treatment of diseases. Cost saving does not constitute a significant clinical advantage, hence will not be taken into account when deciding whether a product meets the clinical criteria for priority assessment.

The sponsor of a medicine may request priority assessment if: the medicine is indicated for the treatment or diagnosis of a serious, life-threatening or severely debilitating disease or condition for which other treatment options are limited. Sponsors may also request priority assessment to address an out-of-stock situation or withdrawal from the market of alternative medicines and it is essential that access to that treatment is maintained.

Requests for priority assessment can only be made by the New Zealand sponsor or distributor of the product.

Sponsors are encouraged to provide support for claims of significant clinical need by submitting material such as letters of support from PHARMAC, clinicians and consumer support groups.

(B) Significant potential cost savings

A request for priority assessment of a medicine on the basis of potential cost savings can normally only be made by or with support from PHARMAC. Such requests are considered by the Minister's delegate who, where appropriate, instructs Medsafe to undertake a priority assessment of the application.

(C) Medicines manufactured in New Zealand for export

A request for priority assessment of a medicine that is to be exported should be made by the sponsor at the time the application for consent is lodged. The request should include the following information:

- a statement that the medicine (prescription or non-prescription) is being manufactured in New Zealand for export. (It is not necessary for the medicine to be produced exclusively for export.)
- a declaration that early approval of the medicine in New Zealand would facilitate access to the intended export market(s).

Applications given priority assessment under the “exported medicines” criterion will have a lower priority than applications granted a priority under criteria A or B.

The Manager Product Regulation decides which applications are accepted for priority assessment.

2.8.2. Processing of priority assessment applications

Applications that have been accepted for priority assessment will be processed earlier and faster than normal applications. Applications granted priority assessment on clinical grounds or on cost saving grounds will be given a higher priority than applications granted priority assessment on export grounds.

Applications granted priority status are allocated to an evaluator and becomes that evaluator’s next piece of new work.

If concerns are raised during the evaluation a request for further information will be issued. The granting of priority assessment status is conditional on applicants responding to a request for information within 28 days.

If a sponsor considers that Medsafe's request cannot be responded to within 28 days, they should first contact Medsafe to ensure that the request has been correctly interpreted. In cases where the sponsor cannot obtain the information requested within the 28 day timeframe, it can still be provided after this deadline but the priority status of the application will be revoked.

Medsafe considers the 28 day response time to be reasonable as applications should be complete before lodgment. A further benefit of truncating the response time is that the application can be referred back to the original evaluator in most circumstances, with increased efficiency in concluding the evaluation.

Section 3: Changed Medicine Notifications

Section summary

This section outlines the format and data requirements for applications for Ministerial consent to distribute changed medicines.

Legislation to read in conjunction with this section:

[Medicines Act 1981](#), [section 24](#): Distribution of changed medicines restricted

3.1. Format for Changed Medicine and Related Product Notifications

When submitting a Changed Medicine Notification (CMN) or Changed Related Product Notification (CRPN) the relevant forms and fee schedules are published on the Medsafe website. CMN Form A should be used for Type I and Type II products while CMN Form B should be used for Type III products.

Each CMN or CRPN involving a material change must be accompanied by a CMN or CRPN form and summary sheet, providing administrative details and outlining the changes being notified. A separate sheet should be completed for each product and all sections must be completed. Applicants should submit one copy of the form, summary sheet and any supporting documentation.

Legislation requires that the initial evaluation must be completed within 45 days. The standard timeframe for initial evaluation of a CMN is 21 days. CMNs are not eligible for priority assessment. CMNs referred under Section 24(5) of the Medicines Act 1981 are subject to the timeframes of NMAs.

The fees applied depend upon the type of product and the amount of evaluation involved.

- Type I: Lower-risk medicines and related products**
- Type II: Intermediate-risk or Higher-risk medicines other than biological or biotechnological products (but including antibiotics and like substances derived from micro-organisms)**
- Type III: Biological, or biotechnological products (ie, vaccines, serums and allergens, medicinal products derived from human blood or plasma, immunological medicinal products, and products derived from biotechnology)**

If the same change(s) has been approved by another regulatory authority in Australia, Europe or North America and that authority's evaluation report is available, a copy should be included with the CMN.

Where an applicant applies for consent to distribute a new medicine or related product and notifies the Director-General of changes to a currently marketed product at the same time the documentation must be kept separate. It is not acceptable to combine a CMN or CRPN with an NMA or NRPA.

Medsafe will not accept further changes to a CMN or CRPN after it has been submitted (except, perhaps, to indicate or clarify changes consequential to the changes notified in the original CMN

or CRPN). If further (non-consequential) material changes are intended a new CMN or CRPN and fee are required.

Note that when Medsafe issues formal consent for a change to a medicine or related product, only those changes specifically identified and applied for in the CMN or CRPN form are covered by the consent. Material changes included in any accompanying documentation but not specifically identified in the CMN or CRPN form and consequently not assessed as changes, are not included in any consent that may be granted for the CMN or CRPN.

Consequential changes are grouped with some material changes for the purpose of fees calculations. However, these changes must be identified separately and supported by appropriate data or documentation, if relevant.

Each change included in a CMN or CRPN is assessed separately. In some cases, Medsafe may consider that only some of the proposed changes can be approved. This may be because the supporting data submitted with the CMN or CRPN do not justify the other changes proposed. In this situation, if the sponsor is unable to supply acceptable data to support the proposed change(s), a recommendation to withdraw those changes from the CMN or CRPN will be made to the sponsor. This will enable consent to be granted for the approvable changes. Partial consent for some of the changes, with other changes assessed later, is not Medsafe's current practice. Any proposed changes withdrawn from a CMN or CRPN can be resubmitted as a new CMN or CRPN at a future date when the required supporting data are available. New fees will apply to this new notification must be accompanied by a new fee applying to those particular changes

3.2. Data Requirements for Changed Medicine or Related Product Notifications

The data required to support a Changed Medicine Notification (CMN) or Changed Related Product Notification (CRPN) is essentially the same as that required for the corresponding section of a New Medicine Application.

Except in the case of a changed label, updated specifications or data sheet, no data are required to be submitted with a Self-assessable Change Notification. The applicant must, however, hold the data required to show that the change is acceptable and must be able to supply the data to Medsafe on request.

In the case of other changes, the following data should be provided, and if not provided, may be requested by the evaluator:

Formulation

Certificates of Analysis issued by the finished product manufacturer for two or three representative batches of any new excipient if that excipient is not controlled in accordance with a recognised pharmacopoeial monograph.

Comparative dissolution data for the proposed new and currently approved finished products using a discriminatory test, must be supplied for tablets and capsules. The data need to establish that there are no significant differences between the new and original formulations.

Certificates of Analysis for the finished product manufactured using the proposed new formulation. At least one batch should be full production scale unless otherwise justified, while the other batches should be at least pilot scale manufactured using full production scale equipment.

Bioequivalence data if required (see note below).

Stability data if required (see note below)

If the formulation involves a change to the preservative system, then additional data may be required such as:

Proof of anti-microbial efficacy of the finished product at expiry.

Test methods (and validation data) for the determination of preservative content at finished product release.

Stability data (including microbial quality).

Note: The following changes are considered unlikely to have an impact on the stability or bioavailability of an immediate release or modified release solid oral dose form:

- Removal, replacement or reduction in the amount of a colouring or flavouring agent.
- A change in the percentage content of any of the following excipients provided that:
 - the change in the amount of an individual excipient does not exceed the maximum allowable change for that excipient as shown in the table below, and
 - the total additive change to all non release-controlling excipients is not more than 5% of the total formulation, and
 - the total additive change to all release-controlling excipients in a modified release dose form is not more than 5% of the total formulation, and
 - the total weight of the dosage form is still within the previously approved range.

Excipient	Maximum allowable change (as percentage of total weight)
Filler	5%
Disintegrant: Starch	3%
Other	1%
Binder	0.5%
Lubricant: Calcium stearate	0.25%
Magnesium stearate	0.25%
Other	1%
Glidant: Talc	1%
Other	0.1%
Film coat	1%

If a product undergoes a series of stepwise formulation changes, bioavailability data will be required if the overall change exceeds the limits stated above.

When an application is made for approval of a change to the formulation of a solid oral dose form, and the change falls *within* the criteria above, a bioequivalence study and stability study are not required to be submitted with the change notification. For any formulation change that falls

outside the criteria given above, the applicant must either provide stability and bioavailability data, or provide adequate justification for not doing so.

Site of manufacture (Active ingredient)

Either a Drug Master File with accompanying “letter of access”, or a EDQM Certificate of Suitability with accompanying “letter of access”, or (if the finished product is “low risk”) Certificates of Analysis for representative batches of active ingredient issued by the finished product manufacturer.

For prescription medicines acceptable evidence of GMP (from a Medsafe-recognised authority – see [Part D, Section 5](#)) for the new active ingredient site of manufacture must also be submitted.

Site of manufacture (Finished product)

GMP certification for the new site, if available, or other acceptable evidence of GMP compliance at the site (see [Part D, Section 5](#)).

Appropriate validation of the process at the new site must be submitted to demonstrate that product manufactured at this site meets the currently registered requirements for in process controls and the finished product specifications.

Description and validation of quality control test methods where there is a change in test procedures or the laboratory testing the product.

Certificates of Analysis for representative batches of finished product manufactured at the new site. At least one batch should be full production scale unless otherwise justified, while other batches should be at least pilot scale manufactured using full production scale equipment.

Comparative dissolution data using a discriminatory test, must be supplied for tablets and capsules. The data need to establish that there are no significant differences between product made at the old and new sites.

Relevant stability data must be generated for batches produced at the new site as required by GMP. Medsafe may request the Company to provide accelerated stability data for a particular medicine where stability is known to be a problem or where changes in stability could have clinical consequences. The relevant stability data need not necessarily be supplied prior to the issue of consent for the change of site. However, if stability data are not supplied, the Company must provide written assurance that stability data will be generated and Medsafe notified immediately if there are any significant problems identified or if the data indicate that the stability of product from the new site is different from that made at the original site to the extent that the shelf life of the medicine would be affected.

If the application complies with the FDA’s Guidance for Industry on Scale-Up and Post-Approval Changes (SUPAC) requirements, this is also acceptable.

Manufacturing process (Active ingredient)

Description of changed manufacturing process and in-process controls.

Certificates of Analysis for representative batches of active ingredient manufactured using the new process.

Manufacturing process (Finished product)

Description of the changed manufacturing process including validation and in-process controls.

Certificates of Analysis for representative batches of finished product manufactured using the proposed process. At least one batch should be full production scale unless otherwise justified, while the other batches should be at least pilot scale manufactured using full production scale equipment.

Comparative dissolution data for representative batches of the finished product using a discriminatory test, must be supplied for tablets and capsules. The data need to establish that there are no significant differences between the product manufactured using the new and original manufacturing processes.

Stability data or confirmation that stability data will be collected. Relevant stability data must be generated for batches produced using the new process as required by GMP. Medsafe may request the Company to provide accelerated stability data for a particular medicine where stability is known to be a problem or where changes in stability could have clinical consequences. The relevant stability data need not necessarily be supplied prior to the issue of consent for the change of process. However, if the data are not supplied, the Company must provide written assurance that stability data will be generated and Medsafe notified immediately if there are any significant problems identified or if the data indicate that the stability of product from the new process is different from that made at the original process to the extent that the shelf life of the medicine would be affected.

Bioequivalence data if required.

Specifications/test methods (active ingredient and finished product)

Justification for specification changes.

Validation of any changed test methods.

Certificates of Analysis for the active ingredient or finished product demonstrating the ability of the company to meet specifications.

Packaging

Packaging materials specifications.

Stability data if the packaging may be expected to be less protective than the currently approved packaging.

New and extended indications

Justification or supporting clinical data (as appropriate) and a draft revised data sheet.

3.3. Self-assessable Changes

One copy of the CMN or CRPN form should be submitted for a material change that is self-assessable.

Medsafe **acknowledges** but does not formally “approve” or issue a “consent notice” for **Self-Assessable Change Notifications** (SACNs). SACNs are subject to audit and then, if a SACN is found to be unsatisfactory, Medsafe advises the sponsor and requests rectification of the unsatisfactory or inappropriate aspect(s) of the SACN (eg, by submission of a formal CMN). Once the CMN is evaluated and found to be satisfactory, a consent notice is issued for that CMN.

Labels and data sheets

When a self-assessable change is made to a label or data sheet, the appropriate checklist and /or declaration must be completed by the applicant and submitted with the CMN or CRPN form, along with copies of the previously approved data sheets or new labels. See [Part 5: Labelling of Medicines and Related Products](#) and [Part 10: Requirements for Information for Prescribers and Consumers](#) for further details.

A CMN or CRPN is not required when the only change to a label is the classification statement (as long as no other changes to the label are required as a consequence of reclassification). In this case all that is required is a copy of the new label for inclusion in Medsafe’s product file.

Change of sponsor

When a change in sponsor for a product(s) is to be made, a self assessable CMN or CRPN is required providing details of the change and all of the products involved. Letters or other documentary evidence from both the new and old sponsor (or the manufacturer, if that is more appropriate) confirming the arrangement should be submitted with the CMN or CRPN.

Changes to secondary reference standards

The quality control of biological/biotechnological products often includes assays for determination of biological activity, potency or other specific properties. The assay test methods may be based on comparative assessment of test samples against preparations of reference standards. Two types of standard preparations exist: primary standards, which are established and well characterised biological reference preparations issued by international organisations such as the WHO and NIBSC; and secondary standards, which are preparations with activity calibrated relative to the relevant primary standard. Secondary standards are variously referred to as in-house working/reference standards and subsidiary standards. A SACN is acceptable for the replacement of secondary standards used in biological assays for Type III (biological or biotechnological) products provided all of the following conditions are met:

- an assurance is provided that no other changes have been made, other than the replacement of the secondary (in-house) reference standards, or other self-assessable changes
- the use of the new in-house standard is qualified following a protocol previously approved by Medsafe. The protocol must have been approved as part of the NMA or as a subsequent (assessable) CMN to change the secondary (in-house) reference standard
- the currently approved dossier makes reference to the fact that self-assessable CMNs will be used to inform Medsafe of changes to secondary (in-house) reference standards, with Medsafe having the option to request and review additional supporting information or data as it sees fit
- an assurance is provided that Medsafe will be advised immediately of any aberrant results that arise during routine use of the secondary (in-house) standards, or GMP issues identified regarding management of in-house standards
- the self-assessable CMN confirms all of the above, and is sent, along with any relevant data, prior to routine use of new secondary (in-house) reference standard.

A change of this kind should be submitted using CMN Form B, 'Test methods and specifications – Grade 6' (self-assessable).

A CMN 'Test methods and specifications – Grade 3' is required if any of the above requirements are not met.

3.4. Changes Not Requiring a CMN or CRPN

3.4.1. Changes in Pharmacopoeial Specifications

A CMN or CRPN is **not** required for updating of specifications for an active ingredient, excipient or finished product to conform to the most recent edition of the relevant pharmacopoeial monograph. Manufacturers are expected to keep their specifications in line with any revisions to those monographs. However, a CMN or CRPN **is** required if there is a change from the specifications of a monograph in one pharmacopoeia to that in another pharmacopoeia, or from in house specifications to a pharmacopoeial monograph (or *vice versa*).

3.4.2. Changes in names of manufacturers or packers

When the name of a manufacturer or packer is changed but there are no changes to the address or the manufacture or packing processes a CMN or CRPN is not required. Instead, the sponsor should advise Medsafe by letter so that Medsafe can update its records. A CMN is required if the change in name is a result of a change in ownership.

When there is a change in name of a manufacturer or packer, each sponsor that uses the site is responsible for notifying the change to Medsafe.

3.4.3. Updates to Drug Master Files

Drug Master Files (DMFs) should be updated periodically to reflect any changes. Sponsors should ensure that such updated DMFs (together with a list of changes made), or (at least) details

of any changes made, are forwarded to Medsafe. Medsafe considers the list of changes made and, if the changes are such that formal evaluation of them is required, the sponsor will be required to submit a formal CMN.

3.4.4. Updates to Plasma Master Files

Plasma master files should be updated at least annually. For guidance regarding the content of the update, refer to EMEA/CHMP/BWP/3794/03 Rev.1 (Guideline on the Scientific Data Requirements for a Plasma Master File (PMF) Revision 1). The sponsor is required to forward a hard copy of the revised PMF (plus any associated evaluations and approvals) to Medsafe which then considers the changes and, if action is required, advises the sponsor accordingly. This will include a request for submission of a CMN to cover introduction of new establishments for supply of plasma.

3.4.5. Changes to Working Cell Banks or Working Seeds

Manufacture of many Type III (biological or biotechnological) products involves the use of cultured cells, either as hosts for propagation of viruses (eg. mammalian cell culture), or themselves to express active molecules (eg. recombinant mammalian cell culture, recombinant or wild type bacteria or fungi). These cells are often passaged from the Master Seed (or Master Cell Bank) to give a Working Seed (WS) or Working Cell Bank (WCB). The same strategy is used to lay down Working Seeds for bacteria and viruses used in manufacture of vaccines.

An advisory letter (with no payment), rather than a CMN, is required for production (and use) of a new lot of WCB or WS (henceforth referred to simply as WCB) **if all of the following conditions are met:**

- The currently approved dossier does not dictate use of a particular lot or batch of the WCB.
- The new WCB is derived from the previously approved Master Cell Bank, is manufactured using facilities, materials and processes already approved by Medsafe for this purpose, and meets a specification approved by Medsafe when tested following methods approved by Medsafe. Current pharmacopoeial requirements for the WCB, and its methods of manufacture and testing, must also be met.
- The use of the new WCB is qualified following a protocol already approved by Medsafe for this purpose, and the company provides an assurance that any apparent aberrant results seen during routine full-scale use will be communicated immediately to Medsafe.
- No deleterious changes to the product's adventitious agent safety profile are introduced by use of the new WCB. Current Notes for Guidance and ICH Guidelines concerning minimising contamination with adventitious agents (viral and TSE) are complied with. The currently approved dossier makes reference to the fact that advisory letters (rather than CMNs) will be used to inform Medsafe of changes to WCB, with Medsafe having the option to request and review further information as it sees fit. It could be that the dossier includes commitment to provide certain data (eg. results of testing and/or preliminary qualification) with the advisory letter.
- The advisory letter confirms all of the above, and is sent, along with any relevant data, prior to routine use of the WCB commencing.

A CMN (Bulk active methods of manufacture) is required to lodge the above information, and to propose the future use of advisory letters, unless this is covered in the NMA.

A CMN (Bulk active methods of manufacture) is also required if any of the above requirements are not met, or if changes are to be made to any details of manufacture or testing, or if any changes are to be made to Master Seed or Master Cell Bank.

3.4.6. Addition or change to New Zealand Site of Product Release

To add or change the New Zealand Site of Product Release a CMN or CRPN is not required. Instead, the sponsor should advise Medsafe by letter so that Medsafe can update its records.

3.5. Referral of a CMN under Section 24(5)

[Section 24](#) of the Medicines Act sets out restrictions on the distribution of changed medicines. Subsection 5 permits the Director-General of Health to refer a medicine (that is the subject of a CMN) to the Minister in certain circumstances. Such a referral occurs when a CMN is so large or complex that the changed product should not be allowed to be distributed until the changes have been fully evaluated.

Examples of CMNs that are typically referred under Section 24(5) include:

- additional indications or extensions to the current indication or dosing regime
- new sites of drug substance manufacture (involving a new Drug Master File)
- 'Grandmother's axe' products (when changes are so significant that the proposed product no longer resembles the approved product)
- failure to respond to requests for information.

The timeframe for a CMN referred under Section 24 (5) of the Medicines Act is 200 calendar days from the date of referral, the same as an NMA.

Changed Medicine Notifications referred under Section 24(5) of the Medicines Act 1981 are susceptible to the same eligibility criteria for priority assessments as NMAs (see Section 2.7.1).

Section 4: New Related Product Applications

Section summary

This section outlines the format and data requirements for applications for Ministerial consent to distribute new and changed related products.

Legislation to read in conjunction with this section:

[Medicines Act 1981](#), Part VII (sections 94-96: Related Products)

[Medicines Amendment Regulations 2011](#), Regulation 23: New [Regulation 58A](#) of the Medicines Regulations 1984

4.1. Excluded Products

Regulation 58A of the Medicines Amendment Regulations 2011 has introduced an exclusion from the medicines legislation for some products that were previously related products (eg, anti-dandruff shampoos, anti-acne skin care products and dentifrices).

The criteria for exclusion are described in the Regulations and related to the claims made for the product and the active ingredients used. Applicants should determine whether their product meets the criteria for exclusion and decide if their product is a related product or medicine before making an application.

4.2. Data Requirements for New Related Product Applications

An application for consent to distribute a new related product should be accompanied by the following data:

Summary of the Dossier

Administrative data, including purpose and directions for use

Labels

Manufacturing Quality Assurance

- (Note that GMP certification is required for related products intended to be taken internally but need not be provided for other dose forms).

Chemical, Pharmaceutical & Biological Documentation

Composition and presentation of product

- (Note: Product Development Pharmaceuticals are not required.)

Method of preparation

Specifications for active ingredients

- (Control tests on excipients need not be supplied.)

Quality control of the active ingredient(s) both as the raw material and in the finished dose form.

Specifications for the finished product

- (Validation data should be provided to confirm that the proposed test methods work satisfactorily for the characteristics that establish the therapeutic nature of the product concerned.)

Representative batch analytical data for the finished product.

Stability

- (Required only for products taken internally, or otherwise, if relevant.)

Other information (if relevant)

Section 5: Proprietary Ingredients

Medsafe has generated a register of Proprietary Ingredients to ensure accurate and up to date information is held on Proprietary Ingredients used in pharmaceutical products marketed in New Zealand.

5.1. Registration of a Proprietary Ingredient with the database

The Medicines Act 1981 required sponsors to disclose all ingredients in a product including the formulation and manufacturing controls on Proprietary Ingredients. This information is used to register Proprietary Ingredients within the Medsafe database. The database is independent of product files thereby allowing several sponsors to quote a common Proprietary Ingredient in their formulations.

The following information is required to register a Proprietary Ingredient:

- the full name of the Proprietary Ingredient
- any unique identification number associated with the Proprietary Ingredient
- the manufacturer name
- the qualitative formulation
- the quantitative formulation
- a copy of the specifications from either the sponsor or the manufacturer.

The following information will not be acceptable in fulfilling the above requirements:

- material safety data sheets – these do not list all the ingredients
- the Proprietary Ingredient's ARTG number from Australia's TGA – Medsafe cannot obtain the required information from the TGA.

The sponsor can request the supplier of the Proprietary Ingredients to provide the information directly to Medsafe for confidentiality. The information can be submitted electronically or by post.

Any Proprietary Ingredient that is notified to Medsafe is registered with the database and allocated a unique reference number. This reference number can be quoted in all subsequent applications instead of submitting the required information. Reference numbers are sent to companies upon registration.

5.2. Proprietary Ingredient Form

The Proprietary Ingredient form has been developed to act as an 'audit trail' between companies that market registered medicines, the Proprietary Ingredient supplier and Medsafe to assist all parties in monitoring the information flow. Medsafe regards the use of the form as voluntary.

The form has been prepared in response to difficulties in collecting the confidential information from Proprietary Ingredient suppliers. The sections to be completed in the form have been developed based on the information required to register a Proprietary Ingredient in the database.

[A copy of the form is available from the Medsafe website.](#)

5.3. Registration Search

Proprietary Ingredients can be checked for registration by searching the 'ingredient field' in the Medsafe Product/Application database. [This is accessed on the Medsafe website.](#)

The Proprietary Ingredient name can be entered to search for registration.

- Colours, coating agents and inks are registered as brand name, colour, ID number
eg, Opadry white 123456
- If the colour or ink does not have a brand name, special categories or colour and inks are used to register them
eg, Edible ink 123456
- Flavours are registered as type, flavour, ID number
eg, Orange flavour 123456

Alternatively, the finished product name can be searched in the Medsafe Product/Application database under the 'trade name' field to check for Proprietary Ingredient registration. The information for registration will appear in the product details under the excipient section.

Registered Proprietary Ingredients have a reference number alongside the Proprietary Ingredient name. If a Proprietary Ingredient is registered but is not linked to your product, please contact Medsafe to confirm the use of the Proprietary Ingredient in your product.

Section 6: Classification and Reclassification of Medicines

Superseded. Please refer to the "Classification of Medicines" section of the Medsafe website
<http://www.medsafe.govt.nz/profs/class/clascon.as>



MEDSAFE

NEW ZEALAND MEDICINES
AND MEDICAL DEVICES
SAFETY AUTHORITY

A BUSINESS UNIT OF
THE MINISTRY OF HEALTH

New Zealand Regulatory Guidelines for Medicines

Part D:
**Guides to preparing the content
of your application**

Edition 6.16
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(consolidation of fifth edition and subsequent updates)

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Section 1: General Requirements for Applications

1.1. Who should apply

The [Medicines Act 1981](#) requires that a **New Medicine Application (NMA)**, **Related Product Application (NRPA)**, **Changed Medicine Application (CMN)** or **Related Product Notification (CRPN)** is lodged by or in the name of a manufacturer, importer or proprietor resident in New Zealand. The New Zealand resident manufacturer, importer or proprietor may be an individual or a company and is designated the “sponsor” (or “licence holder”) for the product concerned. The sponsor is legally responsible for all aspects of the product in New Zealand, including any regulatory action relating to it. The sponsor is responsible to ensure the accuracy of any information submitted to Medsafe in support of any NMA, NRPA, CMN or CRPN.

An overseas pharmaceutical company wishing to market a medicine or related product in New Zealand therefore needs to have a New Zealand-based subsidiary or appoint a local individual or company as New Zealand agent to act for them in New Zealand as sponsor for the product concerned. The New Zealand subsidiary or agent is the sponsor responsible for the product, including any supply of the product under [Section 2](#) of the Medicines Act and any recall of the product from the market.

An NMA or NRPA or CMN or CRPN is submitted to Medsafe in the name of the sponsor. An overseas branch of the company or a local or overseas regulatory affairs consultant may act on the sponsor’s behalf and prepare the paperwork for an application and submit it to Medsafe. For administrative purposes, the identity of the “applicant” depends upon the circumstances:

- ☞ Many applications and notifications are prepared, signed and forwarded to Medsafe by an employee of the sponsor (eg, a regulatory affairs manager or associate). In this case the applicant is the sponsor.
- ☞ Some applications and notifications are prepared and submitted on the sponsor’s behalf by an independent regulatory affairs consultant who signs the documentation as if he or she was an employee of the sponsor. In this case the applicant is the sponsor.
- ☞ Some applications and notifications are prepared and submitted on the sponsor’s behalf by a local or overseas consultant who signs the documentation, not as an employee, but in his or her own right as a contracted agent of the sponsor. In this case the consultant (not the sponsor) is the applicant.
- ☞ Some applications and notifications are prepared and submitted on the sponsor’s behalf by an overseas branch of the company. An employee of the overseas company signs the documentation and forwards it to Medsafe. In this case the overseas branch of the company is the applicant while the New Zealand branch is the sponsor.

Where a local or overseas regulatory affairs consultant or an overseas branch of a company acts on behalf of the sponsor in submitting an NMA, NRPA, CMN or CRPN, a letter (or copy of a previous letter) from the sponsor confirming the consultant’s or overseas company’s authority to act on the sponsor’s behalf should be forwarded to Medsafe, either with the application/notification or separately.

All Medsafe correspondence relating to the application or notification will be sent to the applicant, irrespective of whether the applicant is also the sponsor, unless the applicant specifically requests otherwise.

Joint applications in which all or part of the data are shared, may be made by two or more sponsors. It should be clearly indicated in the application that each sponsor supports the shared use of the data. This may be indicated by the covering letter(s) being signed by all sponsors. The letter(s) must identify the person to whom questions and other correspondence relating to the application should be addressed.

Such joint applications commonly relate to one product to be distributed under two or more brand names. For administrative purposes, each brand name is treated as a separate product. However, the application fee is calculated as for one principal product attracting a full fee with each additional brand name attracting a smaller additional fee as if it was for an “additional name” of the principal product.

1.2. Language

The medicines legislation requires applications and supporting data to be written in English. Documents in languages other than English (eg, GMP certificates and manufacturer’s licences) may be included in the application dossier provided they are accompanied by a notarised English translation.

1.3. Format

The preferred format for NMAs and NRPA’s is the [ICH Common Technical Document \(CTD\)](#) or the older “EU format” for applications submitted in the European Union. If an application dossier in ICH or EU format is available, this should be submitted unchanged **except** for Part IA (Administrative Data) which should be presented using the form given in Part E, [Section 1.1](#) or [Section 1.2](#). Where an application dossier in ICH or EU format is not available, Part IA should be submitted and the remainder of the data package supporting the NMA should preferably be assembled as far as reasonably possible to coincide with the ICH or EU format. Regardless of the format, a detailed Table of Contents must be provided to assist evaluators in their assessment.

Effective 1 September 2006, the required dossier format for all Intermediate-risk and High-risk New Medicine Applications will be the Common Technical Document (CTD) format.

Module 1, the country specific module, should include:

- ☞ A covering letter
- ☞ The current New Medicine Application Form
- ☞ A comprehensive table of contents
- ☞ Copies of proposed labelling
- ☞ A draft datasheet and package insert (where applicable)
- ☞ Evidence of GMP
- ☞ Copies of European Certificates of Suitability (where applicable)
- ☞ Letters of Access to required Drug Master Files (where applicable)

Incorrectly formatted dossiers will be returned to the applicant at the applicant's expense.

Applicants should contact Medsafe prior to submission of their medicine dossier if they have any questions regarding the required format.¹

1.4. Individual Patient Data

Normally individual patient data from clinical trials need not be included in an application dossier (except in the case of bioequivalence studies where the individual plasma/serum concentrations and derived pharmacokinetic data are to be supplied). However, tabulated individual patient data may be included in clinical trial documentation if the applicant considers it appropriate.

Before an application is lodged, applicants should ensure that individual patient data (case report forms) are available in a format acceptable for submission in the EU or USA, and indicate in the application that these data are available. Individual patient data not already supplied may be requested during the evaluation period.

Where not already presented in the Clinical Expert Report, overall numbers of clinical trial patients and treatment subgroups should be tabulated and submitted with Part I of the application.

1.5. Covering Letter

All NMAs and NRPAs should be accompanied by a covering letter. A covering letter is not required for a CMN or CRPN unless the sponsor wishes to provide information additional to that given in the CMN or CRPN form. Section 4 of the relevant CMN or CRPN form must be completed *in full* with the currently approved details and the proposed changes described, whether or not a covering letter is included.

For higher-risk medicines, the covering letter should indicate whether there are any significant differences in the product, its indications, or the data submitted in New Zealand, Australia and Europe. An explanation for such differences should be given.

¹ Section 6.3 CTD Formatted Dossiers (July 2006)

1.6. Submitting an Application or Notification

The applicant must ensure that the application dossier is complete. Medsafe does not carry out detailed checking of dossiers for completeness upon receipt. They are accepted in good faith and placed in the appropriate evaluation queue. There may be situations when some data (eg, final stability data) may not be available until later. If this is the case, the situation should be explained and justified in a covering letter and an estimate of when the information can be expected to arrive at Medsafe should be given.

Once an evaluator commences the assessment of the application or notification and finds that the dossier is incomplete in critical information (eg, an accompanying DMF or equivalent data, appropriate bioequivalence data, or stability data sufficient to support a reasonable shelf-life are missing) and no adequate explanation for the omission or indication of when the information can be expected to be supplied has been provided, the application may be rejected at this point and the application fee may not be refunded. Applicants, therefore, are strongly advised to check carefully all applications and dossiers of supporting data for completeness before submitting material to Medsafe.

All data, including supplementary data, must be submitted on A4 sized paper and should be bound in sturdy ring-binders (or other types of binders from which pages can be removed and replaced) that do not spill their contents when opened. Each part of the application should contain a detailed Table of Contents.

Applicants wishing to submit data in electronic form should discuss the requirements with the Evaluation Team Leader.

One copy of all applications and supporting data should be submitted. For applications to be considered by the **Medicines Assessment Advisory Committee (MAAC)**, additional copies of the dossier of supporting data will be requested by the MAAC Secretary when required (usually about 2 months before the [MAAC meeting](#) to which the application has been assigned).

Applications for approval of new or changed labels or data sheets must be accompanied by the appropriate notification form, checklist and a signed declaration. (See [Part 10](#)).

Send completed applications (with supporting data and the appropriate fee) to the Manager:

Postal Address: Medsafe
PO Box 5013
Wellington

Street/Courier Address: Medsafe
Level 6
Deloitte House
10 Brandon Street
Wellington

Boxes containing volumes of data must be sturdy enough to provide adequate protection to their contents. They should also not exceed the weight that can be comfortably lifted.

The courier should be advised **not** to deliver the boxes to the reception desk on the 6th floor of Deloitte House on 10 Brandon Street. Instead, the courier should contact reception to notify their arrival and arrange access to the locked data storage area on a higher floor of the building.

The fee cheque should not be enclosed in one of the cartons of data. It should accompany the covering letter and Part IA for an NMA or NRPA, and accompany the CMN or CRPN form for a change notification.

Explanatory Note: Return of Incomplete Dossiers

As a result of receipt of an increasing number of incomplete dossiers and dossiers that are incorrectly labelled, paginated or indexed, Medsafe advises that as of 1 August 2006, it will reject and return all such dossiers at the applicant's expense. (Please note the updated [Part D, Section 1.3](#) regarding preferred format for new Prescription Medicine applications.)

When sending dossiers please ensure that:

- ☞ all dossiers that are delivered in boxes are labelled clearly on at least two sides that are visible when the box is stacked.
- ☞ the label includes:
 - ☞ the box number and the total number of boxes associated with the application (eg, Box 1 of 5)
 - ☞ the name of the product
 - ☞ the TT50- file number, if applicable
 - ☞ the contents of each box by module and volume number
 - ☞ modules 1 & 2 are included in Box 1 (if more than one box), together with a cover letter if there is one, and the payment details. If possible, the label of box 1 is identifiable by colour.
 - ☞ each box only contains documentation relating to one New Medicine Application.
 - ☞ each box weighs less than 15Kg.

Please note that any fee paid for dossiers that are returned will be non-refundable, and if no payment is apparent in the application the company will be invoiced. If a company wishes to resubmit, this will be a new application with a new fee. Incomplete dossiers will be returned to the applicant at the applicant's expense.

Applicants should contact Medsafe prior to submission of their medicine dossier if they have any questions.²

² Explanatory Note on Section 6.6 Submitting an Application for Notification (Oct 2006)

1.7. Updating the Data Package

While a product is being evaluated, applicants should notify Medsafe of:

- € any rejections or withdrawals of applications in other countries
- € any serious adverse effects observed for the first time, or at a frequency which has become a concern.

Applicants should consider withdrawing an application if, during the evaluation period, significant new data become available that are contrary to the use of the medicine.

Applicants are encouraged to update stability data for New Higher Risk Medicines during the evaluation process provided the additional data can be received by Medsafe no less than 2 months before the product is due for consideration by the MAAC. This will allow the data to be taken into account in determining the shelf-life at approval and so reduce the need for changes later.

1.8. Sponsors' Responsibility to Retain Copies of All Documents

Sponsors are expected to retain a copy of *all* documentation submitted to Medsafe and all correspondence relating to NMAs, NRPAs, CMNs and CRPNs, and data sheets. They are also expected to retain copies of product specifications and certificates of analysis for each batch of their products distributed in New Zealand.

In the event of a company merger or takeover, regulatory files should be transferred to the new sponsor.

1.9. Technical Guidelines to be Followed

The technical data requirements for applications for consent to distribute new and changed medicines in New Zealand are closely aligned with those currently applying in the European Union. The European requirements are published by the European Commission (EC) as the [Rules Governing Medicinal Products in the European Union](#). Various other documents have been published as additions and amendments to these Rules by the [Committee for Proprietary Medicinal Products \(CPMP\) Working Parties](#) as 'Notes for Guidance'. Medsafe also recognises the technical guidelines published by the United States Food and Drug Administration. These CPMP and FDA documents are listed on [EMEA](#) and [FDA](#) Internet web sites and may be downloaded from there (see Subsections [1.9.2](#) and [1.9.3](#) below).

The International Conference on Harmonisation (ICH) has also developed tripartite guidelines for use by regulatory authorities in the EU, USA and Japan. When these reach the final stage of adoption by the ICH they are normally adopted by the EC, USA and Japan as additions to, or replacements for, their guidelines.

Once ICH, CPMP or FDA guidelines are formally adopted and come into force in the EU or the USA they are recognised by Medsafe.

Medsafe also recognises relevant guidelines published in the British, European and United States Pharmacopoeia and, where relevant, the guidelines published by the World Health Organisation and the [Australian Therapeutic Goods Administration](#) (TGA).

While there are different administrative procedures applying in New Zealand and Australia, there is substantial harmonisation of the data requirements for evidence of quality, safety and efficacy of medicines and the grounds on which consent for distribution is granted in the two countries. Consequently, there are considerable similarities between the requirements of Medsafe and the Australian TGA. However, there are Australian-specific requirements for some aspects of the quality control and stability data that are not relevant to New Zealand. New Zealand has a cooler climate than Australia and, consequently, the same stability data may support a longer shelf life for room temperature storage in New Zealand (<25°C) than in Australia (<30°C).

It is recognised that, in some circumstances, a different approach from that described in a guideline may be appropriate. However, where an applicant chooses to submit a data package that does not meet the relevant guideline, that decision should be explained and justified in the dossier submitted in support of the application. The following situations are possible grounds for departing from current guidelines:

- ☞ scientific development
- ☞ circumstances unique to the product in question
- ☞ adoption by the company of an acceptable approach which had not previously been considered by Medsafe
- ☞ sufficient alternative studies having been conducted which satisfy the criteria of quality, safety and efficacy.

In assessing the chemical, pharmaceutical and biological data submitted with new medicine applications and changed medicine notifications, Medsafe generally follows the technical guidelines published by the International Conference on Harmonisation (ICH), the European Commission and its Committee for Proprietary Medicinal Products (CPMP), and the United States Food and Drug Administration (FDA), as well as the technical guidance provided by the British, European, and United States Pharmacopoeia (which Medsafe regards as essentially equivalent and equally acceptable standards). Where appropriate, Medsafe also takes notice of guidelines published by the World Health Organisation (WHO) and the Australian Therapeutic Goods Administration (TGA). Medsafe recognises these overseas guidelines from the dates on which they come into force internationally.

Medsafe expects toxico-pharmacological studies and clinical studies supplied in support of any new medicine application or changed medicine application to have been carried out in accordance with the internationally accepted standards of Good Laboratory Practice and Good Clinical Research Practice.

Where a product or ingredient is controlled according to a pharmacopoeial monograph, the specifications are to be updated to reflect any revisions to the monograph concerned. Where a pharmacopoeial monograph exists, this is considered to be the minimum requirements for the product or substance.

Guidelines and pharmacopoeia are constantly evolving as a result of scientific developments and harmonisation of the requirements of the major overseas regulatory authorities. Medsafe

endeavours to keep abreast of such developments and keep its evaluation policies in line with “best international practice”.

Where an ICH guideline exists for a particular aspect of a medicine (eg, impurity limits, validation of analytical procedures, stability) and has been adopted by the European, US and Japanese regulatory authorities, conformity to this guideline is the normal requirement for applications submitted to Medsafe. Applicants should ensure that the data in their application dossiers comply with these ICH guidelines. It is recognised, however, that older medicines may have been developed before publication of the ICH guidelines. The data packages for these products may not meet current ICH guidelines, but do meet earlier CPMP or FDA guidelines. In this situation, the available data should be submitted for evaluation. The data will be acceptable if they can be seen to be effectively equivalent, although not identical, to those which would meet the requirements of the ICH guidelines.

Where no ICH guideline exists for a particular aspect of a medicine, data will normally be acceptable if they comply with the requirements of the CPMP and/or FDA guidelines. These guidelines are generally equivalent in intent, if not always in their details.

The ICH, CPMP and FDA guidelines are listed on and available for downloading and printing from these organisations’ web sites (see below).

1.9.1. ICH guidelines

The ICH has developed and published numerous guidelines relating to the quality, safety and efficacy of medicines. Copies of these guidelines may be obtained from:

ICH Secretariat
c/o IFPMA
30 rue de St-Jean
PO. Box 9
CH-1211 Geneva 18
Switzerland
Fax: +41-22-345 8275
Web: <http://www.ich.org>

ICH guidelines may also be obtained in electronic form (printable pdf format) via the Internet from the following address: <http://www.ich.org> and select “Publications” and “Guidelines”.

1.9.2. CPMP guidelines

The European Commission (EC) has issued various directives relating to medicinal products. The Commission’s CPMP and its veterinary equivalent (the CPVP) has applied these directives in developing a set of rules which have been published in series of volumes entitled *Rules Governing Medicinal Products in the European Union*. Volumes 2B, 3A, 3B and 3C are applicable to New Zealand as well.

Volume 1 details European Union pharmaceutical legislation and EC directives and, therefore, is generally not relevant to applications submitted in New Zealand.

Volume 2 is in 3 parts (A, B and C) and details the procedures for marketing authorisation in the European Union (Vol. 2A), the presentation and content of application dossiers, summaries of product characteristics and expert reports (Vol. 2B) and regulatory guidelines (Vol. 2C). Medsafe prefers that application dossiers submitted in New Zealand are in the EU format as described in Volume 2B.

Volume 3 is also in 3 parts (A, B and C) and contains technical guidelines relating to the various sections of the dossier, namely: Quality and Biotechnology (Vol. 3A), Safety, Environment and Information (Vol. 3B), and Efficacy (Vol. 3C). Numerous other specific guidelines have been drafted or finalised by the CPMP Working Parties and issued as separate 'Notes for Guidance'.

Volume 4 details the EC requirements for good manufacturing practices (GMP) for medicinal products for human and veterinary use.

Volumes 5, 6, 7 and 8 detail European pharmaceutical legislation, regulatory procedures and technical guidelines for veterinary medicinal products.

Volume 9 details European requirements for pharmacovigilance of both human and veterinary medicinal product.

Printed copies of the European Commission's *Rules Governing Medicinal Products in the European Union* and the individual 'Notes for Guidance' may be obtained from:

Office for Official Publications of the European Communities
2, rue Mercier
L-2985 Luxembourg
Fax +352-488573 or +352-486817

Printed copies of the *Rules Governing Medicinal Products in the European Union* may also be obtained from:

Hunter Publications
58a Gipps Street
Collingwood
Victoria 3066
Australia
Fax: +61-3-9419-7154

Alternatively, the *Rules* may be downloaded in printable electronic form (pdf format) from the Internet site: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/eudralex_en.htm

Individual 'Notes for Guidance' may be obtained in printable electronic form (pdf format) from the following Internet site: <http://www.emea.europa.eu/home.htm>

1.9.3. FDA guidelines

The US FDA has published numerous guidelines dealing with all aspects of medicines. Copies of FDA guidelines may be obtained from:

Office of Training and Communications

Division of Communications Management
Drug Information Branch
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20858
USA
Fax: +1-301-827-4577

Most FDA guidelines relevant to New Zealand requirements may also be obtained in printable electronic form (pdf format) from the following Internet address:

<http://www.fda.gov/cder/guidance/index.htm>

FDA guidelines relating to biological and biotechnological products may be obtained from:

<http://www.fda.gov/cber/guidelines.htm>

1.10. Proprietary Names

The proposed proprietary name for a new medicine or related product must be clear, unambiguous, not unacceptably similar to, or likely to be confused in any way in print, handwriting or speech with, another medicine or related product currently registered in New Zealand, and not misleading in any way with regard to the nature, composition, purpose, uses or effects of the product.

Section 2: Bioequivalence / Interchangeability

Section summary

This section:

- defines the choice of reference product for a bioequivalence study
- lists the products for which comparative bioavailability is required
- discusses interchangeability and the list of interchangeable multi-source medicines

2.1. Introduction

To be approved for distribution in New Zealand, a multi-source prescription medicine must usually be bioequivalent to the appropriate **New Zealand Reference Product (NZRP)**. Similarly, evidence of bioequivalence will usually be required for changes in products where bioavailability or clinical efficacy may be significantly altered as a result of the change. Evidence of bioequivalence with a reference product is the surrogate used, instead of clinical trial data, to demonstrate safety and efficacy.

Oral dose forms are considered bioequivalent when 90% confidence intervals for the ratios of their geometric mean C_{max} and AUC (from zero time to infinity for single doses or within a dosing interval at steady state) are within the range 0.8 - 1.25 (wider limits, eg, 0.75 – 1.33, may be appropriate for C_{max} in certain circumstances where this can be justified on clinical grounds), and any difference between their T_{max} 's is within clinically acceptable limits.

The above range is the maximum permitted for medicines that present a known or theoretical bioequivalence problem requiring an *in vivo* bioequivalence study. It may be tightened for medicines that have:

- ☞ a narrow therapeutic index
- ☞ known serious dose-related toxicity
- ☞ a steep dose/effect curve
- ☞ non-linear pharmacokinetics within the therapeutic dosage range.

Bioequivalence of metered dose inhalers and other inhaler devices may be established from data establishing physical and clinical equivalence.

Procedures for establishing the bioequivalence of oral dose forms and inhaled products are outlined in Part D, [Section 7](#) and [Section 8](#) respectively.

There is no New Zealand specific guideline for bioequivalence of topical corticosteroid preparations. The US FDA has published a guideline for establishing the bioequivalence of this type of product entitled *Topical Dermatological Corticosteroids: in vivo bioequivalence*.

Note: Where there is any doubt about the appropriateness of a bioequivalence study age, design, choice of reference product, formulation of the reference product, or the formulation of the test product, the applicant is strongly advised to seek Medsafe's advice before submitting the data in support of an NMA or CMN.

2.2. Choice of Reference Product

To establish bioequivalence, the applicant must provide evidence that a multi-source product is bioequivalent to the **New Zealand Reference Product (NZRP)**. In most circumstances, the NZRP is either the innovator product marketed in New Zealand or another product for which Medsafe holds clinical trial and pharmacology data.

There may be more than one reference product, especially where two products have entered the market with clinical trial and pharmacology data. Where there is no obvious innovator or where the innovator product is discontinued, the reference product is the New Zealand market leader.

It is not essential for the batch of reference product used in the bioequivalence study to be sourced in New Zealand. However, when it is sourced outside New Zealand, evidence is required that the foreign-sourced batch has an identical formulation to the New Zealand market product. Such evidence usually includes most or all of the following:

- ☞ appearance
- ☞ dimensions (mean and individual data for 10 dosage units)
- ☞ mean weight and weight uniformity for 20 dosage units
- ☞ dissolution profiles (mean and individual data for 6 dosage units) at 3 different pHs across the gastro-intestinal range 1 to 7.5
- ☞ Fourier transform infra-red (FTIR) spectra of samples, recorded either as KBr pellets or as pressed powders in a diamond cell, scaled so that the strongest band in each spectrum is the same height and the spectra can be overlaid for comparison
- ☞ powder X-ray diffraction (XRD) spectra
- ☞ results (where practicable) of qualitative and quantitative analyses of the excipients.

For changed innovative medicines the reference product will be the formulation previously approved and marketed.

2.3. Bioavailability Data Requirements

2.3.1. Product types that require comparative bioavailability data

If a new prescription medicine is intended to be substituted for a product already on the market, bioequivalence with this product should be shown or justified. Comparative bioavailability studies should be carried out when lack of bioequivalence may be therapeutically significant. Therefore, comparative bioavailability studies are carried out if there is a risk of lack of bioequivalence and/or a risk of therapeutic failure or diminished clinical safety.

Comparative bioavailability studies are required for the following types of product:

1. Systemically-acting oral immediate release products with any of the following characteristics:
 - ☞ indicated for serious conditions requiring an assured therapeutic response
 - ☞ narrow therapeutic index
 - ☞ steep dose-response curve
 - ☞ pharmacokinetics complicated by:
 - variable absorption
 - absorption less than 70%
 - non-linear pharmacokinetics
 - pre-systemic elimination/first pass metabolism greater than 70%
 - ☞ high ratio of excipients to active ingredients
 - ☞ unfavourable physico-chemical properties (eg, low solubility, poor permeability, metastable crystalline form, instability)
 - ☞ documented evidence of bioavailability problems either for the particular medicine or other medicines with similar formulations or whose active ingredient(s) have similar chemical structures
 - ☞ no relevant data available, unless justification by the applicant that an in vivo study is not necessary
2. Non-oral and non-parenteral immediate release products designed to act systemically
3. Modified release products with a systemic action
4. Fixed combination products with systemic action

2.3.2. Justifying not submitting comparative bioavailability data

Where comparative bioavailability data are normally required in an application but the sponsor wishes to omit the data, justification for the omission is required.

The following issues should be addressed in the justification (copies should be provided of any literature cited):

- ☞ What is the water solubility of the medicine?
- ☞ What is the nature of the dosage form?
- ☞ For reformulations and applications for approval of a new strength or flavour of an already approved product, how similar are the formulations of the various products? For different strengths, are the formulations direct scales?
- ☞ For reformulations and applications for approval of a new strength of an already approved product, how do dissolution profiles of the various products compare? For multi-source products, this may include a dissolution comparison of each strength with the corresponding

strength of a market leader. If the multi-source and the market leader are supplied in different strengths, a comparison is still possible in terms of percent label strength dissolved against time, but the justification will be less powerful.

- ☞ Is there a first pass effect and is it significant?
- ☞ Are the pharmacokinetics linear?
- ☞ How wide is the margin between the minimum effective and minimum toxic plasma concentrations?
- ☞ What are the clinical consequences of lack of bioequivalence or variable bioavailability (eg, increased dose leading to toxicity or decreased dose leading to inefficacy)?
- ☞ Are any special claims made in labelling or prescribing information about the absorption profile?

2.3.3. Medicines not requiring comparative bioavailability data

New Medicine Applications for the following dose forms or product types do not usually need to include comparative bioavailability data or a justification as to why the data are not required.

- ☞ Over-the-counter (OTC) medicines.
- ☞ Simple aqueous solutions intended for intravenous injection. Micellar or liposomal solutions are not regarded as 'simple' solutions.
- ☞ Solutions, complex or simple, which do not contain pharmacologically active ingredients, eg, artificial tears, contact lens solutions, lubricants, irrigation solutions and cleansing solutions.
- ☞ Aqueous injections containing the same active ingredients and excipients in the same concentrations, and administered by the same route(s), as an already approved product.
- ☞ Oral solutions containing the same active ingredients in the same concentration as an oral solution already approved, and where the excipients do not significantly affect gastric passage or absorption of the active ingredients.
- ☞ Powders for reconstitution where the resultant solution meets the criteria for one of the five solution groups above.
- ☞ Topical or locally acting solutions that have the same formulation.
- ☞ Products containing therapeutic substances which are not systemically or locally absorbed (eg, antacids, anthelmintics, barium sulphate enemas or oral suspensions, non-biodegradable ion exchange resins or other non-biodegradable long chain polymers, powders in which no ingredient is absorbed). If there is doubt as to whether absorption occurs, a study or justification may be required.
- ☞ Vaccines (clinical trial data are always required for vaccines)
- ☞ Nebuliser solutions
- ☞ Nasal sprays intended for local action
- ☞ Medicinal gases
- ☞ Monoclonal antibodies

- ☞ Dialysis solutions
- ☞ Products for which an acceptable correlation has been shown between the dissolution rate *in vivo* and *in vitro*, and the dissolution rate *in vitro* of the new product is equivalent to that of an already approved market leader under the same test conditions as were used to establish the correlation.
- ☞ A product that differs from an already approved product only in the strength of the active substance does not require bioavailability data provided all of the following five conditions are met:
 - the pharmacokinetics of the medicine are linear within the therapeutic dose range, **and**
 - the products are direct scales (or in the case of small strengths, the ratio between the excipients is the same), **and**
 - both products are produced by the same manufacturer using the same manufacturing process, **and**
 - a bioavailability or bioequivalence study has been performed with the original product, **and**
 - under the same test conditions, the dissolution rate *in vitro* is the same.

Note: Products are said to be ‘direct scales’ only if the same granulate or mixture of powders is used to manufacture the various strengths, but the products are compressed or filled at varying weights corresponding to the various strengths.
- ☞ Products for which the application includes well-performed clinical trials (for the patient population and indication applied for) which establishes efficacy comparable to that of the innovator/market leader product. These products may be approved for distribution even though establishing therapeutic equivalence and interchangeability with the innovator/market leader product is considered a separate issue

2.3.4. Changes not requiring further bioequivalence testing

The following changes to already approved products do not usually require comparative bioavailability data or a justification for the lack of data.

Immediate release tablets, capsules and immediate release compressed implants, suppositories and pessaries:

- ☞ Minor adjustments to the quantities of currently used hydrophilic excipients, including hydrophilic lubricants/glidants, where dissolution profiles of the new and old formulations have been shown to be in the same range
- ☞ Minor changes to the content of talc where dissolution profiles of the new and old formulations have been shown to be in the same range.

For detailed guidance on what constitutes a minor or major change to these products see the [US FDA guidelines](#):

Guidance for Industry - Immediate Release Solid Oral Dosage Forms, Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation

Guidance for Industry - SUPAC-MR: Modified Release Solid Oral Dosage Forms, Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation.

☞ Moulded suppositories and pessaries:

Minor quantitative changes in the currently used excipients where the dissolution profile is in the same range as previously, and

Either

- ☞ Microscopic imaging of particles has shown no visible change in size distribution and morphology (particle sizing may also be conducted by other suitable means such as a Hegmann gauge).

Or

- ☞ It has been demonstrated that particle size and polymorphic form of the active raw material are unaltered. If the method used to check polymorphic form has not been validated, at least two methods should be used including at least one of differential thermal analysis and differential scanning calorimetry. This does not apply where the active is in solution at any stage during manufacture of the finished product, or if it is in solution in the finished product or is present as liquid globules.

For detailed guidance on what constitutes a minor or major change to these products see the [US FDA guidelines](#): *Guidance for Industry - Nonsterile Semisolid Dosage Forms, Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Release Testing, and In Vivo Bioequivalence Documentation.*

☞ Ointments, creams, lotions:

Minor changes in the quantitative content of currently used excipients.

For detailed guidance on what constitutes a minor or major change to ointments and creams see the [US FDA guidelines](#): *Guidance for Industry - Nonsterile Semisolid Dosage Forms, Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Release Testing, and In Vivo Bioequivalence Documentation*

☞ Oral Liquids:

- ☞ Minor changes to the nature or quantity of excipients in simple aqueous solutions, particularly where evidence is provided to show that the osmolality has not been significantly affected
- ☞ Minor quantitative changes to currently used excipients in aqueous suspensions where evidence regarding particle size and polymorphism is provided. See “moulded suppositories and pessaries” above.
- ☞ Aqueous solutions for injection:
Addition or deletion of up to 1% benzyl alcohol.
- ☞ Other minor reformulations and minor changes to the manufacturing procedure, where it can be convincingly argued that the change will not affect bioavailability and where relevant, the dissolution profiles *in vitro* under the same test conditions are equivalent.

- ☞ Other changes to manufacturing unlikely to affect bioavailability. For already approved products, notifications to change the site of manufacture, method of manufacture, manufacturing equipment or source of active ingredients do not usually require bioavailability data or a justification for the lack of bioavailability data. However, the following applies:
- ☞ Evidence should normally be provided that the dissolution profile is in the same range as previously for all solid dosage forms (eg, tablets, capsules, suppositories, pessaries, implants) and all modified release dosage forms administered by whatever route (eg, oral, transdermal, vaginal).
- ☞ For semi-solid and liquid products (eg, ointments, creams, lotions, moulded suppositories, pessaries), evidence regarding particle size and polymorphism is required (see “moulded suppositories and pessaries” above).

Medsafe may ask for additional information in certain cases, such as a major change in a method of manufacture for a modified release product. Changes to the synthetic route for an active substance do not require further bioequivalence testing unless the last stage of the synthesis and purification are changed.

Further information on the technical requirements for bioequivalence testing can be found in Part D, [Section 7](#) and [Section 8](#).

2.4. Interchangeability of Multi-source Medicines

This section of the guideline has been modified to reflect the following policy change announced on 7 July 2006:

Publication of the Interchangeable Multi-source Medicines (IMM) List on the Medsafe website is to be discontinued from 7 July 2006.

The reasons for this decision include:

- ☞ The interchangeability list was originally introduced in the early 1990's in response to concerns regarding efficacy and safety by health professionals over the introduction of generic medicines onto the NZ market. It was felt that since this time both patients and health professionals have become far more accepting of the use of generic medicines.
- ☞ An IMM list is unlikely to be a feature of the Australia New Zealand Therapeutic Products Agency.
- ☞ The clinical safety and efficacy of generic medicines is usually established by the use of a biostudy against the innovator product or current market leader. Consequently, for most generic medicines, interchangeability is a 'fait accompli'.
- ☞ The clinical issue of interchangeability of medicines still remains a feature of the evaluation process for new generic prescription medicines. Where new generic medicines are not considered to be interchangeable, the non-interchangeability of a medicine will be required to be stated within a product's data sheet. Medsafe also intends to maintain a list of medicines determined not to be interchangeable and may post this on the Medsafe website if necessary.

Two products are considered to be interchangeable if they meet the following criteria:

Either

- (a) they are pharmaceutically equivalent, **and**
- ☞ their bioavailabilities (rates and extent of absorption) after administration in the same molar dose are similar to such a degree that safety and efficacy are essentially the same.

Or

- (a) they are pharmaceutically equivalent, **and**
- (b) they present no known or potential problems of bio-inequivalence, **and**
- (c) they meet a relevant *in vitro* standard.

2.4.1. Medicines generally considered to be non-interchangeable

The following prescription medicines, and controlled drugs that require a prescription, are *not* considered to be interchangeable owing to a number of pharmacological and pharmaceutical reasons including:

- a) ***the product has a narrow therapeutic index (NTI)***. In cases where the margin between therapeutic and toxic effects is very small, ie, an NTI, the differences in bioavailability between the reference and multi-source product permitted in bioequivalence testing may give rise to significant clinical consequences. Products with an NTI, such as anticonvulsants, antiarrhythmics, theophylline, warfarin, isotretinoin, cyclosporin, thyroxine, etc. are, therefore, not usually considered to be interchangeable.
- b) ***the delivery systems or dose forms of the products are not pharmaceutically equivalent***. Transdermal patches, systemically acting creams or ointments, or suppositories may have been supported by data demonstrating bioequivalence with oral, or other dose forms, as evidence of efficacy. The differences in pharmaceutical form, however, mean that the products are not considered to be interchangeable.
- c) ***there is no acceptable method to establish bioequivalence*** eg, some topical or locally acting medicines. In most circumstances products in this category must demonstrate efficacy on the basis of clinical trials data, and interchangeability with another product cannot be assessed. Multi-source nasal sprays marketed as prescription medicines, however, are an exception to this rule. Nasal sprays are approved for marketing when they meet appropriate pharmacopoeial standards and the majority of the dose is likely to be deposited at the required site. As the delivery device can have a large effect on the amount of dose delivered to the site of action, a statement about the interchangeability of different nasal sprays with the same active ingredients cannot be made unless they have been shown to meet an appropriate bioequivalence standard.

Note: Where there is an acceptable method of establishing bioequivalence, such as skin blanching tests for topical steroid preparations, or comparative clinical trial data have been submitted, the product will be regarded as interchangeable. All OTC nasal sprays are considered interchangeable as they pose no risk of bio-inequivalence).

2.4.2. Medicines gazetted as non-interchangeable

In a small number of circumstances Medsafe may gazette a medicine as non-interchangeable. This may occur where the sponsor for a multi-source product has provided clinical trial data as evidence of efficacy, and so no assessment of interchangeability is possible. Alternatively, the bioequivalence study provided in the application may fail to meet the international bioequivalence criteria administered by Medsafe, by demonstrating that the multi-source medicine is more bioavailable than the comparator reference product.

In such cases Medsafe liaises with its expert committee to assess whether the increased bioavailability is likely to cause any significant difference in the benefit:risk profile of the multi-source product compared to the innovator. If no difference in benefit:risk is expected, and the multi-source product meets all of Medsafe's other safety and quality criteria, the product may be accepted as having been proven to be safe and effective. It may then be approved for distribution in New Zealand but gazetted as non-interchangeable.

This policy recognises the limitations of bioequivalence studies and the fact that “bioequivalence” means that on average two products can be expected to behave the same way, but in some patients there may be significant differences resulting in serious clinical consequences. Non-interchangeability in New Zealand does not mean that the generic medicine is inherently ineffective or defective. Instead, it means that, as a precaution, a patient should be prescribed one brand or the other and, if the medicine has satisfactory results at the prescribed dose, the patient should be maintained on the same brand and not switched back and forth between brands from prescription to prescription.

Where a product fails a bioequivalence test because it has decreased bioavailability compared to the innovator, the product may only be approved on the basis of further clinical trial data.

This approach to the evaluation of multi-source medicines has been in place since the 1991 review of Medsafe’s evaluation procedures.

2.4.3. New Zealand reference product

The **New Zealand Reference Product (NZRP)** is normally the innovator product, but where the innovator is not on the market in New Zealand, the NZRP is the market leader. A product is not included in the list as a NZRP until there is a multi-source product on the market in New Zealand for which bioequivalence with that reference product has been established.

From 7 July 2006, Medsafe will accept biostudies generated against the Australian reference product. Please note that where the Australian reference product cannot be established as being marketed in New Zealand the generic medicine’s datasheet must include the following statement, or words of similar meaning: “This product may not be interchangeable with similar products on the New Zealand market”.³

It is possible to have more than one NZRP for a particular medicine eg, where more than one product has entered the market through provision of clinical trial data as evidence of clinical efficacy. In this situation, a new multi-source medicine may use either of the NZRPs as the comparator product for a bioequivalence study, and would be listed as interchangeable only with the reference product with which it was compared in the study.

³Biostudy Reference Product (Jul 2006)

Section 3: Data Sheets

Superseded. Please refer to [Part 10, Section 2](#) of the *Guideline on the Regulation of Therapeutic Products in New Zealand*.

Section 4: Labelling and Patient Information

Section 4: **Labelling** has been superseded. Please refer to [Part 5: Labelling of Medicines and Related Products](#).

Please refer to [Part 10: Requirements for Information for Prescribers and Consumers](#) for Consumer Medicine Information

Section 5: Good Manufacturing Practice Documentation

Section summary

This section explains when evidence of compliance with GMP is required and what evidence is acceptable.

5.1. When is GMP Documentation Required?

Medsafe requires evidence of **Good Manufacturing Practice** (GMP) compliance for each finished product manufacturing site and packaging site specified in a New Medicine Application or Changed Medicine Notification.

Evidence of GMP compliance is required for products regarded as medicines in New Zealand, whether or not they are considered medicines in the country of origin. For bone cement containing an antibiotic, condoms containing a spermicide, intrauterine contraceptive devices containing copper, and pregnancy tests, all of which are regarded as medical devices overseas but are medicines in New Zealand, evidence of compliance with the relevant medical device GMP requirements in the country of origin (eg, Europe, USA, Australia) is required.

In the case of related products, evidence of compliance with GMP is required for NRPA and CRPNs for products taken internally (eg, throat lozenges, and vitamin and mineral tablets).

Evidence of GMP is **not** required for related products used externally such as fluoride toothpastes and anti-dandruff shampoos. However, evidence is still required to show that the manufacturer complies with an internationally recognised quality system (eg, ISO accreditation).

For bulk active pharmaceutical ingredients evidence that the material is manufactured consistently and produced with acceptable quality is required.

GMP certification, or equivalent documentary evidence, stating the products or product classes for which it has been granted is required for all:

- ☞ manufacturers of the finished product (including manufacturers of intermediate products)
- ☞ sterilisers of the finished product
- ☞ packers of the finished product
- ☞ sites where products are overlabelled

A manufacturing site for a finished product is any site which contributes to a manufacturing operation which converts bulk raw materials to a finished dose form. This includes sterilising sites. A packing site means any site which contributes to a packing operation which places the final dose form into its labelled primary or secondary container.

Manufacturers and/or packers with premises in New Zealand must hold an appropriate current licence to manufacture and/or pack medicines. The licence must have been issued for the site for

the manufacture and/or packaging of the type of product or packaging operation before manufacture or packaging of the product for distribution can commence. Provided they hold such current licences, certification need not be provided with each application or notification.

For overseas manufacturers and packers, Medsafe requires that certification be included with each NMA or CMN which relates to a change of site, even if the site already supplies product to New Zealand and certification has been supplied previously with an earlier application or notification. This reduces delays associated with locating other files, and because it is desirable for the certification to be product-specific and up-to-date.

Acceptable evidence of GMP compliance normally consists of copies of appropriate certificates, manufacturing licences or reports issued by a regulatory authority whose competence is recognised by Medsafe. Details of the documentation that is acceptable and a list of authorities whose competence to certify GMP compliance is recognised by Medsafe is given below in [Section 5.5](#).

The certificate, licence or report should be no more than 3 years old when the NMA or CMN is submitted, and must be no more than 5 years old at the time of approval of the new or changed product for distribution in New Zealand.

If the original documentation was in a language other than English then copies of both the original documents and a certified English translation must be submitted.

If acceptable evidence of GMP compliance is not available, an audit of the site by Medsafe auditors can be arranged at the applicant's request and expense.

5.2. Recognised Documentation

GMP certification recognised by Medsafe can be any document issued by a recognised authority which attests to GMP compliance. Legible photocopies of the documents are acceptable.

Documents should contain the following information:

- ☞ the street address of the site concerned
- ☞ reference to the product or product class
- ☞ reference to GMP acceptability and/or to a GMP audit
- ☞ name and address of the issuing authority
- ☞ date and signature.
- ☞ date of expiry of the certification or licence

The following are examples of acceptable evidence of GMP certification:

- ☞ licence to manufacture issued by a recognised authority where such a licence is issued only where the site is inspected and regularly re-inspected for GMP compliance

- ☞ current registration and entry (for the product, product class or process concerned) of the site in the Australian Register of Licensed Manufacturers
- ☞ United Kingdom Product Licence or Product Licence Variation where name and address of site is shown
- ☞ certification of pharmaceutical product issued under the WHO scheme by a recognised authority which certifies the quality of pharmaceuticals moving in international commerce
- ☞ Canadian Drug Plant Inspection Rating Report
- ☞ a letter or file note from a recognised authority which attests to GMP compliance. The most usual example seen is an extract from FDA files obtained by the manufacturer under the US Freedom of Information Act. It usually states that an audit occurred on the given date and gives the outcome of the audit
- ☞ a certificate issued by the Australian TGA confirming that it has confirmed (eg, with the US FDA) that GMP compliance at the particular site is satisfactory. Note that Medsafe also has access to the FDA's electronic GMP database and can check the GMP status of manufacturing sites inspected by the FDA.

The following are NOT acceptable as evidence of GMP compliance:

- ☞ a licence to manufacture which is not issued by a recognised authority
- ☞ certification issued by a pharmaceutical company - even if the company certifying is not the same as the manufacturer or packer
- ☞ Annual Registration of Drug Establishment (USA). This document is not indicative of GMP compliance.

5.3. Classes of Medicine

Certification should preferably be product-specific. Certification in the WHO format or a manufacturing or product licence listing the product are the most easily obtained examples of this type.

If product-specific certification cannot be obtained, the certification must relate to a medicine or medicines of the same class(es) (see below) as the one which is the subject of the application or notification. A medicine may belong to more than one class. In such cases, the certification should be for a product belonging to the same classes.

- | | |
|------|---|
| I | Medicines containing penicillin |
| II | Medicines containing cephalosporin |
| III | Vaccines or sera |
| IV | Sterile medicines |
| V | Hormones and steroids |
| VI | Microdose preparations (other than vitamins), ie, containing 5 mg or less per unit dose |
| VII | Antineoplastic agents and immunosuppressant agents (other than steroids) |
| VIII | Solid dose forms |
| IX | Recombinant DNA medicines |

X	Metered dose aerosol preparations
XI	Liquids, creams, ointments
XII	Non-metered dose aerosols
XIII	Powders
XIV	Wound dressings
XV	Transdermal patches

5.4. Sites which Manufacture Bulk Active Pharmaceutical Ingredients

Evidence of GMP (or at least evidence that a bulk active pharmaceutical ingredient is manufactured consistently and to acceptable quality standards) is required for *all sites* which manufacture bulk active pharmaceutical ingredients. Such evidence should be included with each application or notification which relates to a change of site.

Applications and notifications must include the name and address of the *actual site of manufacture* and applicants should ensure that there is no confusion between sites of manufacture and addresses of company head offices or brokers. Any documentary evidence of GMP must refer to the actual site of manufacture.

Any of the following are acceptable as evidence for manufacturers of bulk active pharmaceutical ingredients:

- ☞ A GMP certificate or inspection report issued by a recognised authority. Note that not all authorities issue certification for sites manufacturing bulk active substances.
- ☞ A Drug Master File or equivalent data submitted as part of the dossier for a new chemical entity or new biological entity medicine.
- ☞ A European Pharmacopoeial “Certificate of Suitability” for a substance controlled according to the European Pharmacopoeia.
- ☞ Batch analytical data demonstrating consistent quality of the substance produced (accepted as adequate evidence only for lower risk medicines and related products).

Note: A GMP certificate alone is not acceptable as a substitute for a DMF, Certificate of Suitability or batch analytical data where these are normally required.

5.5. Recognised Authorities

GMP certification issued by the authorities listed below is recognised by Medsafe. The authorities listed include the competent authorities in the European Community, member authorities of the PIC and/or PIC/S organisations, and other authorities where Medsafe has information that GMP assessment systems that are compatible with New Zealand expectations exist. The inclusion of all the European Community competent authorities is a consequence of the Mutual Recognition Agreement in Relation to Conformity Assessment that became effective between New Zealand and the European Community on 1 January 1999. Omission of an authority from the list generally indicates that Medsafe has not assessed that authority’s systems, and should not be construed in

any way as an adverse reflection on the competence of the authority itself. The inspectorates recognised by Medsafe are listed below.

Australia

Therapeutic Goods Administration, Commonwealth Department of Health and Family Services

Austria

Pharmaceutical Division, Federal Ministry of Health, Sports and Consumer Protection
(Bundesministerium für Gesundheit und Konsumentenschutz)

Belgium

Inspection general de la Pharmacie, Ministère de la Santé Publique et de la Famille

Canada

Therapeutic Products Directorate, Health Product and Food Branch, Health Canada

Czech Republic

State Institute for Drug Control

Denmark

Medicines Division, Danish Medicines Agency (Sundhedsstyrelsen)

Finland

National Agency for Medicines

France

Agence du Médicament, Ministère de la Santé

Germany

Bundesministerium für Gesundheit

(The individual medicine inspectorates for the different German states and cities, as listed in the Pharmaceutical Inspection Convention List of Inspectors Employed by the PIC/S Competent Authorities, [State, Name of Authority (City)] are as follows:

Baden-Württemberg

Regierungspräsidium Tübingen, Leitstelle Arzneimittel-überwachung Baden-Württemberg
(Tübingen)

Bayern

Regierung von Mittelfranken (Ansbach)
Regierung von Niederbayern (Landshut)
Regierung von Oberbayern (München)
Regierung von Oberfranken (Bayreuth)
Regierung der Oberpfalz (Regensburg)
Regierung von Schwaben (Augsburg)
Regierung von Unterfranken (Würzburg)

Berlin

Landesamt für Gesundheitsschutz, Arbeitsschutz und technische Sicherheit (Berlin)

Brandenburg

Landesamt für Soziales und Versorgung (Wünsdorf)

Bremen

Senator für Gesundheit, Jugend, Soziales und Umwelt-schutz (Bremen)

Hamburg

Behörde für Arbeit, Gesundheit und Soziales (Hamburg)

Hessen

Regierungspräsidium Darmstadt (Darmstadt)

Mecklenburg-Vorpommern

Arzneimittelüberwachungs- und –prüfstelle Mecklenburg-Vorpommern (Schwerin)

Niedersachsen

Bezirksregierung Braunschweig (Braunschweig)

Bezirksregierung Hannover (Hannover)

Bezirksregierung Lüneburg (Lüneburg)

Bezirksregierung Weser-Ems (Oldenburg)

Bezirksregierung Arnsberg (Arnsberg)

Bezirksregierung Detmold (Detmold)

Bezirksregierung Düsseldorf (Düsseldorf)

Bezirksregierung Köln (Köln)

Nordrhein-Westfalen

Bezirksregierung Münster (Münster)

Rheinland-Pfalz

Landesamt für Soziales, Jugend und Versorgung (Koblenz)

Saarland

Ministerium für Frauen, Arbeit, Gesundheit und Soziales (Saarbrücken)

Regierungspräsidium Chemnitz (Chemnitz)

Regierungspräsidium Dresden (Sachsen)

Regierungspräsidium Leipzig (Leipzig)

Sachsen-Anhalt

Landesamt für Versorgung und Soziales Sachsen-Anhalt (Halle a.d. Saale)

Schleswig-Holstein

Landesamt für Gesundheit und Arbeitssicherheit des Landes Schleswig-Holstein (Kiel)

Thüringen

Thüringer Landesverwaltungsamt (Weimar)

For immunologicals: Paul-Ehrlich-Institut, Federal Agency for Sera and Vaccines

Greece

National Drug Organisation (E.O.F.)

Hungary

Drug Inspectorate, National Institute of Pharmacy

Iceland

State Drug Inspectorate

Ireland

Irish Medicines Board

Italy

Pharmaceutical Division, Ministry of Health (Ministero della Sanita, Direzione Generale del Servizio Farmaceutico)

Japan

Pharmaceutical Affairs Bureau, Ministry of Health and Welfare

Liechtenstein

Kontrollstelle für Arzneimittel, Amt für Lebensmittelkontrolle

Luxembourg

Division de la Pharmacie et des Médicaments

Netherlands

Pharmaceutical Inspectorate, Section Pharmaceutical Industry and Trade (Ministerie van Volksgezondheid, Welzijn en Sport, Inspectie voor de Gezondheidszorg)

Norway

Pharmaceutical Inspectorate, Pharmaceutical Department, (Helsedirektoratet Legemiddelavdelingen)

Portugal

Pharmacies and Pharmaceutical Inspections Department (Instituto Nacional da Farmacia e do Medicamento - INFARMED)

Romania

State Institute for Drug Control and Pharmaceutical Research

Singapore

Ministry of Health, National Pharmaceutical Administration

Slovak Republic

State Institute for Control of Drugs

Spain

Ministerio de Sanidad y Consumo, Subdirección General de Farmacéutico

Sweden

Pharmaceutical Inspectorate, Medical Products Agency (Läkemedelsverket)

Switzerland

For sera and vaccines:

Office Federal de la Sante Publique

For other pharmaceutical products:

Office Intercantonal de Controle des Medicaments

United Kingdom

Medicines Control Agency, Department of Health

USA

Food and Drug Administration

Section 6: Ingredients in Medicines and Related Products

Section summary

This section provides details of the format and content of Drug Master Files and Certificates of Suitability. It also details Medsafe requirements for ensuring the freedom of active ingredients and excipients from infective agents and other harmful substances.

Guidelines to read in conjunction with this section:

[CHMP](#): European drug master file procedure for active substances (EU Rules Vol. 3A)

[FDA](#): Guideline for Drug Master Files

[TGA](#): Submission of Data for a Drug Master File (DMF) on an Active Raw Material, Appendix 7 in Australian Guidelines for the Registration of Drugs, Volume 1, July 1994.

[WHO](#): Guidelines for assuring the quality of pharmaceutical preparations made by recombinant DNA technology WHO/PHARM/89.542 BS/89.1609

6.1. Drug Master Files

Active pharmaceutical ingredients (APIs) are commonly manufactured by a company other than the manufacturer of the finished product. In such cases, the manufacture, quality control and stability of the active ingredient are usually described in a '**Drug Master File**' (DMF), submitted to the regulatory authority by the manufacturer of the active ingredient.

Where the active and finished product are manufactured by the same company, information on the production, quality control and stability of the active substance may be submitted as part of the dossier for the finished product rather than in a separate DMF.

In order to refer to the DMF in an application, the applicant must have the written permission of the active ingredient manufacturer who submitted the DMF. A "letter of access" from the active ingredient manufacturer, addressed to Medsafe and indicating clearly the applicant to which it applies must be sent to Medsafe by the active ingredient manufacturer, either with the DMF or separately.

If an active substance manufacturer has supplied (or been asked to supply) a DMF to Medsafe for the registration of a medicine, it is not necessary for a further copy of the DMF (or part thereof) to be provided for the registration of another product sponsored by a different sponsor. However, the active substance manufacturer needs to provide Medsafe with a new letter of access, referring to the previously supplied DMF and the new applicant.

Finished product sponsors are responsible for the quality of their products and the raw materials used to manufacture them. Therefore, applicants should provide written assurance that there is a formal agreement between the active raw material manufacturer and the sponsor which ensures that information will be communicated to the sponsor, and to Medsafe, before any significant change is made to the method of manufacture or specifications of an active raw material used in a product distributed in New Zealand.

Quality control of the bulk active ingredient is carried out by both the manufacturer of the active ingredient and by the manufacturer of the finished product. Testing by the manufacturer of the bulk active ingredient is usually described in a DMF. Good Manufacturing Practice requires the finished product manufacturer to re-test the active ingredient's identity, potency and purity before use in the manufacture of finished products. This testing is usually described in the application dossier for the finished product.

DMFs should be updated periodically to reflect any changes. The sponsor concerned should ensure that either the updated DMF (together with a detailed list of changes made), or details of any changes made, are forwarded to Medsafe. The changes made need to be described in sufficient detail to enable Medsafe to determine if any material changes have been made to the characteristics, manufacture or quality control of the substance concerned and what those changes are. Where formal evaluation of the changes is required, the sponsor will be required to submit a CMN and pay the appropriate fee.

6.1.1. When is a DMF not required?

A DMF is **not** required for:

- ☞ any active substance that is controlled according to the relevant monograph in the European Pharmacopoeia and for which a valid (recently issued) European Pharmacopoeial Commission "Certificate of Suitability" is provided (see [Section 6.2](#) below for details)
- ☞ any active substance predominantly used in a lower-risk medicine (eg, paracetamol) or related product, but if the substance is also used in a higher- or intermediate risk medicine, a DMF or European Pharmacopoeial Certificate of Suitability may be required to support an NMA or CMN relating to that product.
- ☞ common inorganic substances and simple organic compounds available commercially in high purity from chemical supply houses, eg, sodium chloride, magnesium hydroxide, naturally occurring organic acids and their salts (such as ascorbic acid and sodium citrate), sugars (such as dextrose, mannitol), amino acids (even though they may be synthesised rather than being extracted and refined).
- ☞ Simple, unrefined extracts from plant materials.

Although a DMF is not required for these active ingredients, evidence needs to be submitted by the finished product manufacturer that the substance is obtained from a reliable source and consistently complies with the applicable pharmacopoeial or non-pharmacopoeial specifications. Any non-pharmacopoeial specifications need to be assessed to determine their appropriateness and adequacy to ensure the quality of the substance.

6.1.2. Format for a DMF

DMFs compiled using the European or US format are acceptable in New Zealand. If a DMF has already been assessed and approved by an overseas regulatory authority, and the evaluation report is available to the manufacturer, a copy of the full report should be forwarded with the DMF. If the report is not available, the manufacturer should state when and by whom the DMF was assessed and approved.

The DMF may, if required, be presented in two sections, with the first (open) section containing information accessible to the finished dose form manufacturer and the second (closed) section containing information not accessible to the finished dose form manufacturer.

6.2. Certificate of Suitability

Where an active ingredient is described in the European Pharmacopoeia, the manufacturer may submit the DMF (or equivalent documentation) to the European Pharmacopoeial Commission for assessment and issue of a 'Certificate of Suitability' (CoS). This certificate confirms that the purity of the substance, as produced by the manufacturer, is suitably controlled by the monograph in the European Pharmacopoeia. This certificate may then be submitted in lieu of a DMF, obviating the need for regulatory authorities to carry out their own detailed assessment of the data. For details of the certifications scheme, contact the secretariat of the European Pharmacopoeial Commission. Some information is available on the internet site: <http://www.pheur.org>.

Where a CoS is submitted in lieu of a DMF, the sponsor must also provide a written assurance that any conditions attached to the CoS by the European Pharmacopoeial Commission, as well as any agreed additional tests and limits (eg, for polymorphic form, particle size distribution, impurities, etc.) are applied to each batch used in product intended for the New Zealand market.

The European Pharmacopoeial Commission also assesses and issues Certificates of Suitability for substances used as active ingredients or excipients in pharmaceutical products confirming that they comply with European Pharmacopoeial requirements for minimising the risk of transmission of animal spongiform encephalopathies. Medsafe accepts these certificates.

Where a CoS is submitted in lieu of a DMF, the applicant for consent to distribute a medicine in New Zealand must ensure that the CoS is submitted with the written permission of the manufacturer of the bulk active ingredient to be used in manufacture of the finished product for the New Zealand market. Submission of the CoS as part of the dossier of data supporting a new medicine application or changed medicine notification implies, but does not prove, that there is a commercial agreement between the applicant and the active ingredient manufacturer. This agreement between the parties must be confirmed to Medsafe by means of a formal "letter of access" from the active ingredient manufacturer, addressed to Medsafe and clearly indicating the applicant and, where possible, the products to which it applies. The letter of access should also confirm that the active ingredient manufacturer will, if requested, supply direct to Medsafe data relating to the manufacture, quality control and stability of the substance concerned.

6.3. Ingredients of Human or Animal Origin

Guidelines to read in conjunction with this subsection:

ICH Guidelines:

- ☞ Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
- ☞ Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin
- ☞ Quality of Biotechnological Products: Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products

CPMP Guidelines, etc:

- ☞ Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products (CPMP/BWP/1230/98)
- ☞ Position Paper on production of Tallow Derivatives for Use in Pharmaceuticals (CPMP/1163/97)
- ☞ Note for Guidance on Plasma-Derived Medicinal Products (CPMP/BW/269/95)
- ☞ Position Paper on Plasma-derived Medicinal Products: Alt Testing (CPMP/BWP/385/99)
- ☞ Note for Guidance: Virus Validation Studies: The Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses (CPMP/BWP/268/95)
- ☞ The Introduction of Nucleic Acid Amplification Technology (NAT) for the Detection of Hepatitis C Virus RNA in Plasma Pools (CPMP/BWP/390/97)

FDA Guidelines:

- ☞ Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotech-Derived Products
- ☞ Guidance for Industry: Donor Screening for Antibodies to HTLV-II
- ☞ Guidance for Industry: For the Submission of Chemistry, Manufacturing and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use
- ☞ Guidance for Industry: Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeld-Jakob Disease (CJD) and New Variant Creutzfeld-Jakob Disease (nvCJD) by Blood and Blood Products

New Zealand Guidelines:

- ☞ Minimum Standards for the Collection, Processing and Quality Assurance of Blood and Medicines Derived from Human Blood and Plasma (New Zealand, 1998)

If a product contains an ingredient (active or excipient, eg, magnesium or calcium stearate, stearic acid, gelatin) that is, or potentially is, of human or animal origin, or comes into contact with material of human or animal origin during manufacture, the source of the material (or contact) must be declared in the NMA or CMN. If it is of animal origin, evidence must be provided that the product is free from viruses, other micro-organisms and transmissible spongiform encephalopathy (TSE) agents. The guidelines listed above should be followed in preparing the documentation to provide this evidence.

A European Pharmacopoeial Commission Certificate of Suitability is acceptable as evidence of freedom from TSE agents.

6.4. Colouring Agents

The list of colouring agents that are acceptable for use in medicines and related products can be found at:

<http://www.medsafe/regulatory/Guideline/PermittedColourings.asp>

Section 7: Bioequivalence Testing of Oral Medicines

Section summary

This section describes the requirements for designing and conducting a bioequivalence study involving oral tablets, capsules and suspensions, and for analysing and interpreting the results

7.1. Introduction

Several major regulatory authorities overseas have produced guidelines for establishing bioequivalence. These guidelines describe, in varying degrees of detail, the principles involved in the design and conduct of bioequivalence trials, and the analysis of the data. They are continually being updated as experience and knowledge on bioequivalence grows.

Despite considerable international agreement on the general principles of bioequivalence and its establishment, there are differences of opinion regarding some aspects of how some bioequivalence studies should be conducted and how data should be evaluated.

This New Zealand guideline for bioequivalence testing is largely based on the guidelines listed below and what Medsafe regards as best current international practice. The evidence required for bioequivalence usually consists of comparative bioavailability data. In some exceptional cases other data (eg, *in vitro* dissolution) may be sufficient, or the formulation may be such that no comparative testing is necessary.

Situations where comparative bioavailability studies are and are not necessary, and the choice of acceptable reference products for bioequivalence studies, are outlined in Part D, [Section 2](#).

7.2. Important Overseas Bioequivalence Guidelines

The following overseas guidelines have been used as the basis for the New Zealand guideline.

[European Commission Rules Governing Medicinal Products in the European Community Volume III and CPMP Notes for Guidance](#)

Pharmacokinetic studies in man.

Investigation of bioavailability and bioequivalence.

Clinical testing of prolonged action forms with special reference to extended release forms.

Quality of prolonged release oral solid dosage forms.

Analytical validation.

[United States Food and Drug Administration \(FDA\)](#)

The United States FDA guidelines have been published as two “General Information” chapters in the United States Pharmacopoeia XXIII, 1995:

<1088> *In vitro and In vivo Evaluation of Dosage Forms*, USP XXIII, 1995, p 1924.

<1090> *In vivo Bioequivalence Guidelines*, USP XXIII, Seventh Supplement, 1997, page 4022.

[Australian Therapeutic Goods Administration \(TGA\)](#)

Australian Guidelines for the Registration of Drugs, Volume 1, July 1994, Appendix 22B).

[Therapeutic Products Directorate, Health Product and Food Branch, Health Canada](#)

Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part A: Oral Dosage Formulations used for Systemic Effects (1992); and

Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part B: Oral Modified Release Formulations (1997).

World Health Organisation (WHO)

Interchangeable multi-source pharmaceutical products: Multi-source (generic) pharmaceutical products: Guideline on registration requirements to establish interchangeability in WHO Technical Report Series 863, 1996, Annex 9.

7.3. Definitions

Bioavailability is a measure of the rate and extent of absorption of the pharmacologically active form or forms of the active ingredient from a medicine, as reflected by the time-concentration curve in the systemic circulation or by its excretion in urine.

In addition to the extent of absorption, the rate of absorption may be important for many medicines, eg, if a rapid effect is needed or if therapeutic efficacy depends on attaining a certain peak concentration. Rapid absorption may, however, lead to transient side effects or serious toxicity for medicines with a narrow therapeutic index.

In some circumstances, determining the amount excreted or measuring an appropriate pharmacodynamic effect may be the only available method of gauging bioavailability or bioequivalence.

Factors affecting bioavailability include the physico-chemical characteristics of the active ingredient(s) (eg, lipid/water solubility, stability in an acid medium, salt form, particle size), the nature and quantities of excipients, type of formulation (enteric coated, sustained release etc.) and the extent of first pass metabolism by the gut and liver. Patient factors include the timing of the dose in relation to eating, interactions with other medicines taken concurrently, gastrointestinal motility and concurrent disease states.

Bioequivalence is a comparative term. Pharmaceutically equivalent medicines are assumed to be bioequivalent if their bioavailabilities (rate and extent of absorption in the systemic circulation after administration) are so closely comparable that their therapeutic effect, with respect to efficacy and safety, will be essentially the same.

Whether differences in bioavailability between different dose forms, multi-source medicines and reformulations of a dosage form will result in significant differences in clinical effects depends on the nature of the medicine and the mode of its use. For example, quite small differences in bioavailability can lead to serious complications with medicines such as digoxin and quinidine which have low therapeutic indices. For other medicines (eg, benzodiazepines used for their hypnotic or anti-anxiety properties) differences in bioavailability have to be greater in order to produce clear evidence of lack of efficacy or undesirable effects. Since it is impossible to formulate universally applicable rules for bioequivalence, each product needs to be considered individually.

As a general principle, two products may be said to be bioequivalent if the 90% confidence intervals for their mean C_{max} , T_{max} , and AUC (from zero time to infinity for single doses or within a dosing interval at steady state) are within $\pm 20\%$.

The usually accepted criteria for concluding bioequivalence (based on a difference of not more than 20%) are that the 90% confidence intervals for the ratio between the test and reference

geometric means for AUC and C_{\max} (determined using log-transformed data) lie wholly within the range of 0.80 to 1.25 and the non-parametric 90% confidence interval for the difference in T_{\max} between the formulations lies within a clinically acceptable range.

Where close dosage control is critical, a $\pm 20\%$ variation in the rate and extent of absorption may be considered too wide. Tighter limits for permissible differences in bioavailability may be required for medicines that have:

1. a narrow therapeutic index
2. serious, dose-related toxicity
3. a steep dose/effect curve, or
4. non-linear pharmacokinetics within the therapeutic dosage range.

Where an applicant considers a variation in the rate or extent of absorption greater than $\pm 20\%$ is acceptable, this must be explained and justified in the application dossier. The allowable limit will depend upon clinical considerations

Suprabioavailability is the term used when a multi-source product displays a bioavailability appreciably larger than the reference product. When this occurs, reformulation and a final comparative bioavailability study will be necessary. Otherwise, clinical trial data as required for a new chemical entity will be required to support the application for the proposed formulation.

7.4. Variables in a Comparative Bioavailability Study

The blood plasma or serum concentration-time curve of the pharmacologically active substance(s) compared to a reference formulation provides the best measure of bioavailability for medicines with a systemic effect. Where the parent drug substance is an active form and one or more of its metabolites are also active, contribution of the metabolite(s) to the total pharmacological response should be considered in determining whether the metabolite should be measured as well as the parent compound.

Where it is not possible or favourable to measure the active substance(s) in serum or plasma, other less direct measures will be necessary. These could include determining the quantity of the active substance or its metabolites excreted in urine, or measuring pharmacodynamic variables. If data based on measurements other than blood concentrations are presented (eg, saliva or urine concentrations), their relevance must be demonstrated. Usually the quantification of pharmacodynamic parameters is less exact than the determination of concentrations of drug substances and metabolites in body fluids.

For medicines that are mixtures of geometric isomers (eg, clomiphene), both isomers should normally be assayed.

7.4.1. Extent of absorption

The extent of absorption is the fraction of the dose which enters the systemic circulation, as estimated using the "area under the curve" (AUC) of plasma concentration versus time. Extent of absorption can also be estimated from the fraction of the dose excreted in urine as the active form and/or its metabolites.

7.4.2. Rate of absorption

The rate of absorption determines the time delay between administration of a medicine and the time of the maximum (peak) concentration in the fluid being assayed, usually plasma. The rate of absorption can influence the amount of medicine reaching the systemic circulation in the case of a medicine with non-linear kinetics, for example where there is saturable first-pass metabolism.

Other parameters that might provide a better estimate of the rate of absorption (eg, the time to reach a particular concentration or fraction of C_{max}) may be used where appropriate. The use of these parameters must be justified in the dossier.

7.4.3. Pharmacodynamic responses

Where a suitable method for assaying the active form(s) in body fluids is not available, it may be possible to obtain an indirect indication of bioavailability or bioequivalence by repeated determinations of pharmacodynamic or biochemical responses following administration of a medicine.

Some pharmacodynamic variables respond rapidly to a medicine and are easily and accurately measured (eg, heart rate). However, since there is a complex relationship between the onset, intensity and duration of the response and the concentration-time curve of the medicine and/or its metabolites in biological fluids, these variables may not be ideal. In addition, pharmacodynamic measurements may not be sufficiently precise to detect significant differences in bioavailability. For these reasons, bioavailability/bioequivalence studies based on chemical assays of the active form(s) are preferred.

If pharmacodynamic data only are provided, the applicant should outline which other methods were tried and the reasons why they were unsuitable.

The following requirements should be recognised when planning, conducting and assessing the results of a study intended to demonstrate equivalence by measuring pharmacodynamic responses to a medicine:

- ☞ The response which is measured should be a pharmacological or therapeutic effect which is relevant to the claims of efficacy and/or safety.
- ☞ The methodology should be validated for precision, accuracy, reproducibility and specificity.
- ☞ Neither the test formulation nor the reference product should produce a maximal response in the course of the study, since it may be impossible to distinguish differences between formulations given in doses which give maximum or near-maximum effects. Investigating dose-response relationships may be necessary.
- ☞ The response should be measured quantitatively under double-blind conditions and be recorded in a machine-produced or machine-recorded fashion on a repetitive basis to provide a record of the pharmacodynamic events which are substitutes for plasma concentrations. If such measurements are not possible, recordings on visual analog scales may be used. Where data are limited to qualitative (categorised) measurements, appropriate special statistical analyses will be required.
- ☞ Non-responders should be excluded from the study by prior screening. The criteria by which responders versus non-responders are identified should be stated in the protocol.

- ☞ Where an important placebo effect can occur, comparison between products can only be made by *a priori* consideration of the placebo effect in the study design. This may be achieved by adding a third phase, with placebo treatment, in the design of the study.
- ☞ A cross-over design should normally be used where appropriate, but where a cross-over design is inappropriate, a parallel group study design should be chosen.
- ☞ The underlying pathology and natural history of the condition should be considered in the study design. There should be knowledge of the reproducibility of the base-line conditions.
- ☞ In studies where continuous variables could be recorded, the time course of the intensity of the drug action can be described in the same way as in a study in which plasma concentrations are measured. From this, parameters can be derived which describe the area under the effect-time curve, the maximum response and the time when maximum response occurred.
- ☞ Statistical considerations for the assessment of the outcome of the study are, in principle, the same as for bioequivalence studies using plasma concentrations. However, a correction for the potential non-linearity of the relationship between the dose and the area under the effect-time curve should be made, on the basis of the outcome of the dose ranging study.

The conventional acceptance range, as applied for bioequivalence, is not appropriate in most cases. It should be defined on a case-by-case basis and described in the protocol.

7.4.4. Comparative *in vitro* dissolution rate

If it can be demonstrated that there is no suitable ethically acceptable *in vivo* method of establishing bioequivalence, and that such a method cannot be developed, appropriate comparative *in vitro* dissolution data may be an acceptable substitute.

Dissolution studies should possess suitable discriminatory power and be carried out at 37°C and physiologically meaningful pHs. More than one batch of each formulation should be tested. Comparative dissolution profiles, rather than single point dissolution test data, should be generated. The design should include:

- ☞ Individually testing at least six dosage units (eg, tablets, capsules) of each batch. Mean and individual results should be reported along with their standard deviations or standard errors.
- ☞ Measuring the percentage of nominal content released at a number of suitably spaced time points to provide a profile for each batch, eg, at 10, 20 and 30 minutes or as appropriate to achieve virtually complete dissolution.
- ☞ Conducting the tests on each batch using the same apparatus and, if possible, on the same or consecutive days.

Final specifications for routine dissolution testing of the test product should be based on the data generated in this comparative study used to support equivalence of the test and reference products.

7.5. Designing a Comparative Bioavailability Study

Good trial design is essential. Investigators should consider what is already known about the nature and pharmacokinetics of the test medicine. When published data are not available, a pilot study may be necessary to ascertain:

- ☞ the likely T_{max} and C_{max} so that the final design will provide a sufficient number of samples around T_{max} to characterise this parameter and C_{max} adequately
- ☞ the sampling times, in single dose studies, needed to characterise the terminal elimination rate constant and the AUC from the last data point to infinity
- ☞ the adequacy of the assay sensitivity and precision at the intended dose, and
- ☞ the variance in C_{max} and AUC to allow estimation of the number of subjects required to achieve appropriate statistical power

The study should be a balanced cross-over design with appropriate randomisation of the subjects to the different treatment sequences, unless the nature of the medicine means that a return to baseline values is not expected within a reasonable washout period between trial phases. Parallel group design may be suitable, but is often avoided because of the need to increase the number of subjects. The use of a cross-over design does run the risk of sequence effects, but if the study is appropriately designed sequence effects are not usually a problem.

7.5.1. Single dose versus steady-state studies

Single dose studies are appropriate in the majority of cases. A steady-state study may be appropriate in the following circumstances:

- ☞ Where the medicine has a long terminal elimination half-life and blood concentrations after a single dose cannot be followed for sufficient time.
- ☞ Where assay sensitivity is insufficient to follow the terminal elimination phase for an adequate period of time.
- ☞ For medicines which are so toxic that, ethically, they can only be administered to patients for whom they are a necessary part of therapy, but where multiple dose therapy is required, eg, many cytotoxics.
- ☞ For modified-release products where it is necessary to assess the fluctuation in plasma concentration over a dosage interval at steady state.
- ☞ For those medicines which induce their own metabolism or show large intra-individual variability.
- ☞ For enteric-coated preparations where the coating is innovative. For enteric coated preparations, for which the release characteristics have been previously established, a steady-state study is not always required.
- ☞ For combination products where the ratio of plasma concentration of the individual substances is important.
- ☞ For medicines that exhibit non-linear (ie, dose- or time-dependent) pharmaco-kinetics.
- ☞ Where the medicine is likely to accumulate in the body.

In steady state studies, the administration scheme should follow the usual dosage recommendation.

7.5.2. Parameters

The parameters that should be determined in a bioavailability study include:

- ☞ maximum medicine concentration (C_{max});
- ☞ time taken to reach the maximum concentration (T_{max})
- ☞ area under the medicine concentration time curve (AUC)
- ☞ terminal elimination rate constant (k_{el}), and
- ☞ others as appropriate.

These parameters should be calculated using the original concentration vs. time data rather than by curve fitting methods based on compartmental models.

For modified-release products given as a single dose, absorption rate plots should be prepared.

7.5.3. Choice of subjects

To reduce variability caused by disease, bioavailability studies are usually carried out in adult human volunteers of both genders (where appropriate) who are in good health, of average weight (eg, within $\pm 15\%$ of their ideal weight as given in the current *Metropolitan Life Insurance Company Height and Mass Tables*) and in the age range prior to the onset of age-related physiological changes (usually 18-60 years of age).

The supervisory physician should initially obtain a comprehensive recent medicine history (including alcohol intake, smoking and use of oral contraceptive tablets) to exclude possible interference with assays, effects on pharmacokinetics, pharmacological interactions and adverse reactions such as hypersensitivity. As well, the physician should conduct a medical examination and test liver, kidney and haematological function. Psychological characteristics should also be assessed to exclude subjects unlikely to comply with study restrictions and/or unlikely to complete the study.

During the study, the health of the subjects should be regularly monitored so that the onset of side effects, toxicity, or any intercurrent disease may be recorded and appropriate measures taken.

Preferably both genders should be included in the study. However, the choice of gender must be consistent with usage and safety criteria. Women should be required to give assurance that they are not pregnant, nor likely to become pregnant until after the study. This should be confirmed by a pregnancy test immediately prior to the first and last dose of the study.

For a medicine representing a potential hazard in one group of users, the choice of subjects may need to be narrowed, eg, studies on teratogenic medicines should be conducted in males.

Where the risk of side effects or toxicity is significant, studies may have to be carried out in patients who are being treated with the test medicine but whose disease state is stable.

7.5.4. Standardisation of experimental conditions

For medicines taken orally, gastrointestinal conditions should be standardised. Subjects should be fasted for at least 10 hours before and 2-4 hours after dosing, or (if more appropriate for the medicine concerned) the dose should be given with or before/after a standardised meal. Meals consumed after dosing and during the blood-sampling period should be standardised and taken at standardised times after the dose. Any fluids taken with the dose should be the same for all subjects.

Standardisation of posture and physical activity is important to minimise variation in liver blood flow, especially for high clearance medicines, and should approach the conditions likely to be encountered in clinical use. Posture may also affect gastric emptying rates. Therefore, subjects should not be allowed to recline until at least two hours after oral administration of the medicine.

The times at which samples are taken should be similar in all subjects.

7.5.5. Number of subjects

The minimum acceptable number of subjects may be as low as 12, however, the number should be sufficient, in the case of confidence intervals, to give precise estimates of the target parameters and, in the case of hypothesis testing, sufficient to provide the necessary discriminatory power (normally $\geq 80\%$) to detect the maximum allowable difference (usually $\pm 20\%$) in C_{max} , AUC etc. This number, "n", may in many cases be estimated in advance using means, standard deviations and sample sizes from published or pilot data. The calculation formula depends on the statistical method to be used in the analysis of the results at the completion of the study. Computation methods are outlined in [Section 7.10](#) below.

The number of subjects recruited should be sufficient to allow for possible withdrawals or removals from the study. Reasons for any withdrawals (eg, adverse reactions) should be reported and the subject's plasma/serum/blood level data provided.

It is acceptable to replace a subject withdrawn from the study, once it has begun, provided the substitute follows the same protocol originally intended for the withdrawn subject.

If the calculated number of subjects appears to be higher than is ethically justifiable, it may be necessary to accept a statistical power which is less than desirable. Normally it is not practical to use more than about 40 subjects in a bioavailability study. Where calculations suggest that an excessive number of subjects is required, clinical efficacy and/or safety studies are an alternative. The use of a co-administered active ingredient labelled with non-radioactive isotope as a reference, or studies in which treatments are replicated within each subject, may improve discriminatory power for highly variable medicines.

Sequential testing may also be acceptable for studies expected to require a large number of subjects, ie, a study is conducted on a predetermined subset of the required sample and the intended statistical analysis is performed. If the acceptance criteria are met, no further subjects need to be tested. If the acceptance criteria are not met, the results from the first part of the study can be used to determine how many more subjects should be tested. Appropriate statistical tests (eg, sequential t-test) which make allowance for this design should be used. The ethically justifiable maximum number of subjects should also be considered. The final statistical analysis then uses all of the data.

7.5.6. Formulation and quality control data requirements

The detailed formulation of the test medicine used should be provided, or otherwise declared to be identical to that intended for marketing.

For tablets and capsules the test formulation used should originate from either a production-run batch or a pilot-scale batch of at least 10% of the full production scale or 100,000 units, whichever is the greater, and manufactured using full production-scale equipment, unless otherwise justified. In the case of a production batch being less than 100,000 units, the sample should originate from a full production batch.

For suspensions the test formulation used should originate from either a production-run batch or a pilot-scale batch of at least 10% of the full production scale and manufactured using full production-scale equipment, unless otherwise justified.

All medicines used in bioequivalence studies should be manufactured in accordance with good manufacturing practice (GMP).

Quality control data should be provided for both the test and reference products used in the trial. The minimum data required is the batch number, date and scale of manufacture, mean potency, uniformity of potency as determined by assaying 10 individual dosage units and, for tablets and capsules, disintegration time and dissolution profiles determined in aqueous media using standard BP, Ph Eur or USP equipment and procedures. Alternatively, other fully validated dissolution procedures may be used.

Note that any final specifications for *in vitro* dissolution of the multi-source product should be derived from the dissolution profiles for the batch that was found to be bioequivalent to the reference product.

The mean potencies of the test and reference product should not differ by more than 5%.

7.5.7. Number and timing of samples

The number (typically 12-18 blood samples per dose) and timing of samples should be sufficient to enable reasonably accurate estimates of C_{max} and T_{max} , and accurate estimates of AUC and the elimination rate. This information may be obtained in advance from literature data or a pilot study.

The blood sampling period in trials using a single dose of a prompt-release product should extend to at least three elimination half-lives in the terminal elimination phase. Sampling should be continued for a sufficient period to ensure that the area extrapolated from the time of the last measured concentration to infinite time is only a small percentage (normally less than 20%) of the total AUC. The use of truncated AUCs, ie, AUC_t , is undesirable but it may be unavoidable in certain circumstances such as in the presence of enterohepatic recycling where the terminal elimination rate constant cannot be calculated accurately.

There should be sufficient points on the terminal linear part of the log-concentration vs. time curve to calculate the terminal elimination rate constant. The calculation should be based on at least four experimental points at appropriate intervals on the graph. The number of points used to calculate the terminal elimination rate constant should preferably be determined by eye from a semi-logarithmic plot, rather than by allowing a computer program to make the decision.

Intervals between successive data points used to calculate the terminal elimination rate constant should, in general, not be longer than the half life of the medicine.

In steady state studies, sampling should be carried out over a full 24 hour cycle so that any effects of circadian rhythms may be detected, unless these rhythms can be argued not to have practical significance.

In experiments requiring urine collection, it is important that subjects be carefully trained and supervised to ensure that all urine samples are collected according to the protocol. Any urine not collected will invalidate this part of the trial and should be taken into account during analysis of the data. For a 24 hour study, sampling times of 0-2, 2-4, 4-8, 8-12, 12-24 hours are usually appropriate. Where urinary excretion is measured in a single-dose study it is necessary to collect urine for seven or more half-lives.

7.5.8. Fasting and non-fasting studies

Generally a single dose study should be conducted after an overnight fast of at least 10 hours, with a subsequent fast of 2-4 hours following dose administration. However, where the dosage form is a modified release product or when it is recommended that the medicine be given with food, then the influence of food on the bioavailability should be examined. The meal should contain approximately 30-40g of fat as this is likely to cause maximum perturbation to the release and absorption of the medicine. If a recommendation is made about when the medicine should be taken in relation to eating (eg, immediately before food), this should also be taken into account in the design.

Fed studies are also required when fasted studies make assessment of C_{max} and T_{max} difficult.

7.5.9. Medicine administration

The quantity, type and timing of food and fluid taken concurrently with the medicine should be stated, and should be controlled. The time of day the medicine was taken should also be stated, and whether or not the subjects were ambulatory and for how long.

Concurrent use of other medicines, including oral contraceptives, intake of alcohol and caffeine, and smoking cigarettes, should be stated and should be controlled.

Whenever possible and safe, and when given by the same route, the molar equivalent doses of medicine in the test formulation(s) and the reference product should be the same. In studies comparing a modified-release product with a prompt-release product, it may be appropriate for reasons of safety and comparability of plasma concentrations to give the prompt release product in divided doses or as a single, lower dose.

In single dose trials, a sufficient interval should be allowed between the administration of each formulation to ensure that the previous dose of medicine and any metabolites being measured have been completely eliminated. Approximately ten elimination half-lives of the medicine after the peak is usually a sufficient interval. Consideration will need to be given to extending this period if active metabolites with longer half-lives are produced.

In steady-state trials, the dosage regimen should be identical to the established dosage regimen of the reference product. Sampling of blood or urine should be carried out after the plateau (steady state) has been attained. It should be demonstrated that the plateau has been attained. Washout of the previous treatment can overlap with build-up of the second treatment, provided the build-up period is sufficiently long (at least three times the dominating half-life).

The pattern of blood or urine collections, or other sampling procedures, should be standardised for each subject.

Wherever possible the trial design should ensure that the order (sequence) of administering medicine treatments to subjects is randomised and balanced.

7.6. Modified-release Products

This section refers to orally administered modified-release (MR) dosage forms of medicines which do not have complicated characteristics.

7.6.1. Characteristics

A modified-release dosage form is defined as one for which the medicine-release characteristics of time course and/or medicine-release location are chosen to accomplish therapeutic or convenience objectives not offered by prompt-release dosage forms. For the purpose of these guidelines, these include:

- ☞ delayed release
- ☞ sustained release
- ☞ mixed immediate and sustained release
- ☞ mixed delayed and sustained release
- ☞ mixed immediate and delayed release

Generally, these products should:

- ☞ act as modified-release formulations and meet the claims made by the applicant;
- ☞ preclude the possibility of any dose dumping effect;
- ☞ provide a therapeutic performance comparable to the reference prompt-release formulation administered by the same route in multiple doses (of an equivalent daily amount) or to the reference modified-release formulation;
- ☞ produce consistent pharmacokinetic performance between individual dosage units; and
- ☞ produce plasma levels which lie within the therapeutic range (where appropriate) for the proposed dosing intervals at steady state.

If all of the above conditions are not met but the applicant considers the formulation to be acceptable, a case to this effect should be provided.

7.6.2. Parameters

Clinical studies may be required to support claims for the efficacy and safety of MR formulations. Bioavailability data should be obtained for all MR dose forms although the type of studies required and the pharmacokinetic parameters which should be evaluated may differ depending on the active ingredient involved. Factors to be considered include whether or not the formulation represents the first market entry of the drug substance, and the extent of accumulation of the medicine after repeated dosing.

If the formulation is the first market entry of the drug substance, the product's pharmacokinetic parameters should be determined. If the formulation is a second or subsequent market entry then comparative bioavailability studies using an appropriate reference product should be performed.

For medicines where close control is critical the bioequivalence of each strength of the formulation should be established. For other medicines, if the formulations of different strengths are such that the proportion of excipients to the medicine are the same, and adequate documentation of development pharmaceuticals is provided, it is sufficient to establish the bioequivalence of one strength.

For formulations for which the drug substance (or active form) is unlikely to accumulate in the body after multiple dosing ($AUC_{TS}/AUC_{\infty} \geq 0.8$), studies can be performed with single dose administration in the fasting state as well as following an appropriate meal at a specified time. The following pharmacokinetic parameters should be calculated from plasma (or blood or serum) concentrations of the medicine and/or major metabolite(s): AUC_{TS} (AUC over the same interval following a single dose) AUC_t , AUC_{∞} , C_{max} , and k_{el} .

For formulations for which the drug substance (or active form) is likely to accumulate ($AUC_{TS}/AUC_{\infty} < 0.8$), studies should be performed with single dose administration in the fasting state as well as following an appropriate meal. In addition, studies are required at steady state. The following pharmacokinetic parameters should be calculated from single dose studies: AUC_{TS} , AUC_t , AUC_{∞} , C_{max} , and k_{el} . The following parameters should be calculated from steady state studies: AUC_{TCSS} (AUC measured over one dose interval at steady state), C_{max} ,

C_{pd} (the concentration immediately pre-dose), C_{min} , and DF (the degree of fluctuation in concentration as a proportion of the average concentration over the dose interval).

Where the ratio AUC_{TS}/AUC_{∞} , cannot be reliably determined, it is to be assumed that accumulation occurs.

7.6.3. Study design

It is necessary to confirm the bioequivalence of modified release products that are likely to accumulate and those that are unlikely to accumulate, both in the fasted and non-fasting state. If the effect of food on the reference product is not known (or it is known that food affects its absorption), two separate 2-way cross-over studies, one in the fasted state and the other in the fed state, may be carried out. If it is known with certainty (eg, from published data) that the reference product is not affected by food, then a 3-way cross-over study may be appropriate with

- ☞ the reference product in the fasting state
- ☞ the test product in the fasted state, and
- ☞ the test product in the fed state.

7.6.4. Requirements for modified release formulations unlikely to accumulate

This section outlines the requirements for MR formulations which are used at a dose interval that is not likely to lead to accumulation in the body ($AUC_{TS}/AUC_{\infty} \geq 0.8$).

When the MR product is the first market entry of that type of dosage form, the reference product should normally be the innovator's prompt-release formulation. The comparison should be between a single dose of the MR formulation and doses of the prompt-release formulation which it is intended to replace. The latter must be administered according to the established dosing regimen.

When the MR product is the second or subsequent entry on the market, comparison should be with the reference MR product for which bioequivalence is claimed, administered as single doses.

The 90% confidence interval calculated using log transformed data for the ratios (Test:Reference) of the geometric mean AUC (for both AUC_{TS} and AUC_t) and C_{max} (where the comparison is with an existing MR product) should generally be within the range 80 to 125% both in the fasting state and following the administration of an appropriate meal at a specified time before taking the medicine.

The pharmacokinetic parameters should support the claimed dose delivery attributes of the modified-release dosage form.

7.6.5. Requirements for modified release formulations likely to accumulate

This section outlines the requirements for MR formulations that are used at dose intervals that are likely to lead to accumulation ($AUC_{TS}/AUC_{\infty} < 0.8$).

When a modified release product is the first market entry of the MR type, the reference formulation is normally the innovator's prompt-release formulation. Both a single dose and steady state doses of the MR formulation should be compared with doses of the prompt-release formulation which it is intended to replace. The prompt-release product should be administered according to the conventional dosing regimen.

When the MR product is the second or subsequent MR entry, single dose and steady state comparisons should normally be made with the reference MR product for which bioequivalence is claimed.

The 90% confidence interval for the ratio of geometric means (Test: Reference medicine) of AUC (for both AUC_{TS} and AUC_t) and C_{max} (where the comparison is with an existing MR product) determined using log-transformed data should generally be within the range 80 to 125% when the products are compared after single dose administration in both the fasting state and the fed state.

The 90% confidence interval for the ratio of geometric means (Test: Reference medicine) for AUC_{TCSS} , C_{max} , and C_{min} determined using log-transformed data should generally be within the range 80 to 125% when the formulations are compared at steady state.

The pharmacokinetic parameters should support the claimed attributes of the modified-release dosage form.

Pharmacodynamic data may reinforce or clarify interpretation of differences in the plasma concentration data.

Where these studies do not show bioequivalence, comparative efficacy and safety data may be required for the new product.

7.7. Analytical Methods

Analytical methods and conditions of sampling should be fully described, preferably in the form of a standard operating procedure. The chosen analytical methods should be "state of the art" for a given analyte and should be specific and adequately sensitive. Preference should be given to chromatographic techniques such as high pressure liquid chromatography (HPLC) or gas chromatography (GC). Assay validation (see [Section 7.7.1](#) below) should be conducted in the laboratory which generated the study data, using the same analytical procedures. Quality control of assays, while conducting the study, is vital. The investigators' criteria for accepting or rejecting assay data should be stated clearly in the protocol or study report.

If an assay procedure is to be used at different sites, it should be validated at each site and cross-site comparability of results and variability should be established.

Copies of all of the original chromatographic printouts (except for a few examples to demonstrate sensitivity and selectivity) need not be included in the study report. However, the original printouts should be retained by the investigators and be available on request, at least until Medsafe's assessment and approval processes have been completed.

7.7.1. Chromatographic assay validation

Detailed validation data on the specificity, accuracy, reproducibility and sensitivity of the analytical procedure and stability of the analytes in plasma/serum or other applicable body fluids should be included in the study report.

Specificity

Evidence should be provided that the assay does not suffer from interference by endogenous compounds, degradation products, other medicines likely to be present in study samples, and metabolites of the medicine(s) under study. Reference standards of metabolites will frequently not be available, but investigators should address this problem as far as is practicable.

Stability of measured medicine/metabolites

Data should be accumulated which establish the stability of the measured entities (normally parent medicine and/or active metabolites) in the relevant biological environment from time of sampling to assay, under the conditions and duration of storage that apply. The absence of any sorption by the sampling containers and stoppers should also be established.

Minimum quantifiable concentration (MQC)

This is a contentious issue and many approaches are encountered. Terms such as 'limit of detection' and 'minimum detectable concentration' may be misleading in this context since it is typically possible to detect quantities of an analyte substantially below those which can be assigned a meaningful quantitative value. The parameter "three times baseline noise" is often encountered in this context, but reflects what concentration can be detected rather than what can be quantified.

A better approach is to define the MQC as the lowest concentration which has an inter-day coefficient of variation for multiple injections of 20% (as well as this can be measured). It is not necessary to define a MQC if the lowest concentration encountered during sampling has a coefficient of variation of less than 20% during assay validation.

Shape of calibration curve

Linearity is preferred. The shape of the calibration curve should be defined in mathematical terms on more than one occasion (optimally three), preferably over a concentration range from the MQC to a value greater than the C_{max} expected in the study. Calibration standards in the 1,2,5,10,20,50 ----- pattern of concentration are preferable. The coefficient of determination (r^2) should normally exceed 0.99 ($r > 0.995$). Alternative approaches may be used provided justification is supplied.

Assay precision and accuracy

Precision (the degree of reproducibility of individual assays) is established by replicate assays on standards, preferably at several concentrations. Accuracy is the degree to which the 'true' parameter of the medicine is estimated by the assay. Precision and accuracy should normally be documented at three concentrations (low, medium, high) where 'low' is in the vicinity of the lowest concentration to be measured, 'high' is a value in the vicinity of C_{max} and 'medium' is a suitable intermediate value.

Intra-assay precision (within days) in terms of coefficient of variation should be no more than 10%, although no more than 20% may be more realistic at values near the MQC. Inter-assay precision (between days) may be higher than 10% but not more than 20%.

Accuracy can be assessed in conjunction with precision and is a measure of the extent to which measured concentrations deviate from true or nominal concentrations of analytical standards. In general, an accuracy of $\pm 10\%$ should be attained.

Recovery

Documentation of extraction recovery at high, medium and low concentrations is essential since methods with low recovery are, in general, more prone to inconsistency. If recovery is low,

alternative methods should be investigated. Recovery of any internal standard used should also be assessed.

7.7.2. Radioimmunoassays

Similar principles apply to chromatographic and bioassays such as radioimmunoassays and pharmacological procedures, but the details may vary. In addition to the principles outlined for chromatographic methods in [Section 7.7.1](#), the following points relate to radioimmunoassays.

Antibody

The characteristics of the radioimmunoassay depend on the antibody, which varies from animal to animal. Therefore, the following validation details should be repeated for each new batch of antibody: specificity, calibration curve, MQC, precision, and accuracy. It is preferable to use the same batch of antibody for the whole study.

Specificity (cross-reactivity)

Data should be provided that demonstrate which part of the antigen is binding to the antibody, as well as the degree of binding of closely related substances such as metabolites and breakdown products at the antibody titre employed. Specific antibodies should be employed.

Calibration curve

For radioimmunoassays, calibration curves should be fitted to a computer model or transformed by a logit analysis to give a linear relationship between percent bound and concentration of analyte.

Controls

Controls for radioimmunoassay should include blanks comprising pre-dose samples (eg, plasma) from each subject in the study. These should demonstrate that the assay does not indicate the presence of antigen when it is absent. A set of standards from 0 to 90% displacement of label is necessary.

7.7.3. Assay of study samples

The following guidelines describe an acceptable approach to assaying samples.

Daily calibration standards

Calibration standards and a sample blank (eg, plasma) are analysed with each batch of study samples on a daily basis. Two possible approaches are:

- ☞ use three concentrations of standards in triplicate. These can conveniently be the same three concentrations (low, medium and high) used to estimate precision and accuracy in the pre-study validation; or
- ☞ use at least five concentrations of standards from the MQC to the highest concentration encountered in the study.

Calibration standards should be blank samples (eg, plasma) spiked with known concentrations of medicine, and prepared freshly each day from pure reference substance.

Seeded controls should be spaced throughout the batch. Failure to obtain reproducibility and linearity for the daily standards necessitates re-assay of the batch.

Seeded controls

Seeded controls (sometimes called “spikes”) are a valuable component of in-study quality assurance. Control samples at three or more concentrations are prepared in plasma in bulk at the time of pre-study assay validation, or at the time of study sample collection, and are aliquoted into storage vessels.

A control for each concentration is assayed on each occasion that study samples are assayed, and the concentration determined by reference to that day's calibration standards. If the concentration values determined for the controls are not within $\pm 15\%$ of the expected concentrations, the batch should be considered for re-analysis. If not within $\pm 20\%$ of the expected concentrations, the batch should be re-analysed unless there is very good reason not to do so.

Seeded controls, therefore, provide a constant reference point between batches of assays as well as determining whether the medicine is stable under the storage conditions used.

Re-analysis of samples

In most studies some samples will require re-analysis because of aberrant results due to processing errors, equipment failure or poor chromatography. The reasons for re-analysis of such samples should be stated.

When the results of repeat assay differ from the original by more than 15%, a third analysis should be done. When the three analyses indicate that one is spurious, then the average of the other two should be used.

Range of reported values

Concentration values less than the lowest calibration standard should be reported as such and should not normally be used in data analysis. Concentration values greater than the highest concentration used in the linearity studies should be highlighted and accompanied by validation data. Concentration values marginally (up to 20%) above daily calibration standards may be reported if pre-study linearity data extended beyond such values. Concentration values less than the MQC should not be used in data analysis.

7.8. Reporting Data

The concentration of the entities measured in the plasma/serum/blood for each subject, sampling time and formulation should be tabulated. Any deviations (eg, missed samples or late collection of samples) should be clearly identified in these tables. The order in which the formulations were administered to each subject should also be indicated.

Two graphs should be drawn for each subject, and two for the mean values of all subjects. One should be linear and the other a semi-logarithmic plot of the concentrations from the reference and test formulations against sampling times. It is preferable that the semi-logarithmic plots should also display the regression lines which were employed to estimate the terminal elimination rate constants. Alternatively, the number of points used may be indicated or tabulated elsewhere in the study report.

Where plasma concentration data have been generated, the minimum acceptable pharmacokinetic data set for each subject and each treatment is:

1. C_{max}

Generally this should be reported as the highest measured concentration, rather than a value obtained from curve-fitting. The adequacy of such data is a function of the sampling intervals in the vicinity of C_{max}.

2. T_{max}

Generally this should be reported as the time at which C_{max} was observed, using actual sampling times rather than nominal times or values obtained from curve-fitting.

3. AUC_t

The area under the curve to the last sampling time (AUC_t) should be calculated by the trapezoidal rule (the area contribution for each sampling interval is the mean of the concentrations at the beginning and end of the interval multiplied by the length of the interval). The actual sampling times, rather than the nominal times, should be used in the calculations.

4. AUC_∞

For single dose studies, the area under the curve to infinity (AUC_∞) should be calculated using the equation:

$$AUC_{\infty} = AUC_t + C_t/k_{el}$$

where C_t is the plasma concentration at the last sampling time t and k_{el} is the terminal elimination rate constant (where plasma concentrations fluctuate in the terminal region of the curve, it is preferable to estimate C_t from the log/linear plot of plasma concentrations against time).

Tabulations of the proportion of AUC_∞ which is extrapolated, should be provided.

5. k_{el} (or t_{1/2})

Tabulations of k_{el} (or t_{1/2}) should be provided.

6. Other Parameters

Other parameters, such as total urinary excretion, may need to be calculated in some cases.

7.9. Presentation of Summarised Data

All bioavailability parameters should be tabulated, preferably as mean ± standard deviation with the observed range given in parenthesis [eg, AUC_∞ = 25 ± 8 (7-40) ng.h.ml⁻¹]. The units of measurement for the parameter should always be given.

It is important to specify whether measured medicine concentrations refer to plasma, serum or whole blood concentrations.

Where appropriate, AUC and C_{max} and statistical analyses should be normalised for medicine content (mean assay) of both dosage forms. Ratios and confidence intervals should be

normalised if the potencies of the batches of medicines compared differ by more than 3% and/or the calculated confidence intervals lie close to the 80% or 125% limits and normalisation could affect the conclusion. It should be clearly stated in the study report whether data have or have not been normalised.

7.10. Statistical Analysis

The following statistical methods should be used in the analysis of bioavailability trial data. Other methods of analysis may be acceptable, but their use should be justified.

Statistical comparisons between formulations should be based on data derived from individuals and not only on averaged data.

7.10.1. Number of subjects

The minimum acceptable number of subjects is usually 12. However, the number of subjects should provide the study with a sufficient statistical power (usually $\geq 80\%$) to detect the allowed difference (usually 20%) between the test and reference medicines for AUC and C_{max} . This number (n) may, in many cases, be estimated in advance from published or pilot study data using the following formula:

$$n > \frac{2s^2}{\Delta^2} (t_{\alpha} + t_{\beta})^2$$

- α - the required significance level of the study and is equal to 0.05.
- $(1-\beta)$ - the required minimum power of the study and is normally not less than 0.80
- s^2 - the (residual) error mean square from a cross-over ANOVA
- Δ - the allowed difference required to detect as a proportion of the mean for the reference treatment. Δ is generally taken to be (0.2 x mean for reference) and should be in the same units as s.
- t_{α}, t_{β} - the one-tailed Student t distribution values for α and β respectively. The degrees of freedom for t are those of the ANOVA (residual) error mean square.

Where the data are log-transformed, s^2 is the (residual) error mean square from the cross-over ANOVA of the logarithms of the AUC or C_{max} values, and Δ is the logarithm of 1.20.

Because n is unknown *a priori*, it will be necessary initially to use values of the Normal distribution parameters z_{α} and z_{β} in place of the Student 't' distribution parameters t_{α} and t_{β} to derive an estimated value for n and subsequently to perform a simple iteration using this initial estimate to determine n more precisely.

It will be necessary to obtain estimates of s^2 and the reference mean using mean and standard deviation data from the literature and/or from the pilot study. However, as the study variance may differ from the literature or pilot study values, it would be prudent to err on the side of generosity in numbers.

If the calculated number of subjects appears to be higher than is ethically justifiable, it may be necessary to accept a statistical power which is less than desirable. It is usually not ethically justifiable to use more than about 40 subjects.

7.10.2. Analysis of variance (ANOVA)

Analysis of variance (ANOVA) is a technique for investigating how much of the total variability in a set of observations can be ascribed to different causes. The components of the variances are analysed further to tests the null hypothesis H_0 that all of the samples have been drawn from the same population. The alternative hypothesis H_1 is that one or more systematic differences exist.

An ANOVA taking account of subjects, sequence, period (phase) and treatment (formulation) effects should be performed for C_{max} , AUC, T_{max} and other parameters as appropriate to determine if there are any statistically significant differences. A more complex ANOVA may be appropriate in some circumstances, for example if treatments are replicated or if a study has been conducted as two independent phases.

The assumptions underlying such an ANOVA are:

- ☞ Randomisation of samples. (The subjects chosen for the study should be randomly assigned to the sequences of the study.)
- ☞ Homogeneity of variances. (The variances associated with the two treatments, as well as between the sequence groups, should be equal or at least comparable.)
- ☞ Additivity (linearity) of the statistical model. (There should be no interactions between the subject, sequence, period and treatment effects for a standard 2 x 2 cross-over study.)
- ☞ Independency and normality of residuals. (The residuals of the model should be independently and normally distributed.)

The assumptions of normality of residuals and homogeneity of variance in the model are known to be relatively robust. That is, small or moderate departure from each or both of these assumptions will not have a significant effect on the final result. If there is significant evidence of departures from the assumptions then a parametric ANOVA should not be performed on the raw data.

If the assumptions above are not met, the data should be transformed prior to the ANOVA. A non-parametric analysis should be used eg, T_{max} (see below).

Many biological data correspond more closely to a log-normal distribution than to a normal distribution. In particular, the parameters AUC and C_{max} tend to be skewed and their variances to increase with their means. Log transformation is likely to remedy these defects and make the positively skewed distributions more symmetrical. Consequently, AUC and C_{max} data should be log transformed prior to statistical analysis.

The primary comparison of interest in a bioequivalence study is the ratio, rather than the difference, between average parameter data from the test and the reference formulations. Using log-transformation in the analysis allows inferences about the difference between the two means on the log scale. Re-transformation then allows inferences about the ratio of the averages on the original scale. Log transformation thus achieves a comparison based on a ratio rather than on a difference.

Non-parametric analyses (eg, tests based on ranks and computation of 90% confidence intervals for differences between test and reference medicine) should be used for T_{max} data as the observed values are discrete even though the underlying distribution is continuous.

7.10.3. Confidence intervals

It is recommended that confidence interval methods be used instead of hypothesis tests in the estimation of relative bioavailability. The 90% confidence interval for the ratio between the test and reference geometric means for AUC and C_{\max} should be determined using log-transformed data. Confidence intervals wholly within the range of 0.80 to 1.25 will generally be accepted as an equivalence criterion for AUC and C_{\max} .

The non-parametric 90% confidence interval for the difference in T_{\max} between the formulations should lie within a clinically acceptable range.

7.10.4. Power of ANOVA

Calculation of power is necessary whenever two formulations have been directly compared in terms of a null hypothesis of zero difference in conjunction with an ANOVA.

The power of a 2-way ANOVA (accounting for treatments and subjects) to detect a difference between two means amounting to a given fraction of the mean of the reference formulation can be calculated for each bioavailability parameter according to the following equation:

$$t_{\beta,v} = \Delta \sqrt{(n/2s^2)} - t_{\alpha,v}$$

Where:

- 1- β - power
- ν - the degrees of freedom of the ANOVA (residual) error mean square
- Δ - fraction of mean of the reference formulation
- n - number of subjects
- s^2 - (residual) error mean square from the ANOVA
- α - the required significance level of the test and 't' values are one-tailed

Where the data are log-transformed, s^2 is the (residual) error mean square from the cross-over ANOVA of the logarithms of the AUC or C_{\max} values, and Δ is the logarithm of 1.20.

Adequate sensitivity of the statistical test is usually defined as a power of at least 0.8 (80%) with $\alpha = 0.05$. Strictly, the above equation should not be applied to a 3-way ANOVA. In practice, however, since any sequence effect is usually small, it gives a reasonable approximation of the power.

7.11. Data Requirements

The bioequivalence study report should include (as a minimum) the following information:

- ☞ Table of contents
- ☞ Title of study and any relevant reference
- ☞ Names and affiliations of the responsible investigators
- ☞ Signatures of the principal and other responsible investigators authenticating their respective sections of the report

- ☞ Site of the study
- ☞ The period of dates over which the study was conducted
- ☞ Names and batch numbers of the products compared
- ☞ The formulation of the test product(s) or a signed declaration that this was identical to that intended for marketing
- ☞ Results of assays and other pharmaceutical tests (eg, physical description, dimensions, mean weight, weight uniformity, comparative dissolution) carried out on the batches of products compared
- ☞ The full protocol for the study including a copy of the informed consent form and the criteria for inclusion, exclusion or removal of subjects
- ☞ Documentary evidence that the study protocol was approved by an appropriate independent ethics committee or institutional review board and was carried out in accordance with good clinical and laboratory practice
- ☞ Age, height, weight, ethnicity and smoking habit data for the subjects
- ☞ Results of clinical and laboratory screening tests
- ☞ Details of and a justification for any deviations from the protocol
- ☞ Details of any adverse reactions observed
- ☞ Details of any withdrawals from the study
- ☞ Details of analytical methods used, full validation data, quality control data and criteria for accepting or rejecting assay results
- ☞ Representative chromatograms
- ☞ Actual sampling times
- ☞ All individual and averaged assay results presented in a clear way (both tabular and graphical as appropriate)
- ☞ Details of how pharmacokinetic parameters were determined
- ☞ Individual and summarised average pharmacokinetic parameters
- ☞ Details and results of statistical analyses
- ☞ Justification for any departures from conventional statistical methodology.
- ☞ Summary and Conclusions
- ☞ Copies of any literature referred to in the report and not readily available

Section 8: Equivalence Testing of Inhaled Medicines

Section summary

This section describes how to design and conduct a study to compare the clinical efficacy of different formulations or brands of inhaler products.

8.1. Introduction

All applications to market multi-source metered dose inhalers and other inhaler devices must be supported by data establishing physical and clinical equivalence with the reference product. Similarly, applications to market inhalers where a chlorofluorocarbon (CFC) propellant has been replaced with a non-CFC propellant must be supported by data establishing equivalence with the previously approved CFC-containing product.

The following guideline for establishing equivalence of inhalers draws upon the major pharmacopoeia and the following overseas guidelines:

Guidelines on the preparation of Applications to Register Metered Dose Aerosols (Pressurised and Non-pressurised), Appendix 24 in "Australian Guidelines for the Registration of Drugs" [Therapeutic Goods Administration](#): Canberra, July 1994.

Replacement of chlorofluorocarbons (CFCs) in metered dose inhalation products, CPMP Note for Guidance III/5378/93, December 1993.

Draft guidelines on in vivo criteria to establish equivalence of safety and efficacy of a multi-source or second entry drug delivered by metered dose inhaler for drugs intended for delivery to the lower respiratory tract. Health Protection Branch, Health and Welfare Canada: Ottawa, 1992.

The British, European and United States Pharmacopoeia (BP, Ph Eur and USP) include details of the general requirements for quality control and the various physical tests and test equipment appropriate for metered dose inhalers and other inhaler devices.

The specifications for the ingredients, containers and metering devices, the in process controls during manufacture, and the release and shelf-life specifications for the finished product should adequately control the following: defective containers and metering devices, pressure testing, leakage rates, moisture content, active substance delivered per dose (mean and dose uniformity), number of doses delivered, and deposition of dose.

Details of the development of the product and justification for each formulation should be provided in the application dossier. Information should be supplied on the following: excipients chosen, component/propellant ratios, extractables from the elastomeric components of the device, microbial testing, metering valve performance and control, consistency of delivery of dose over time, over the life of the canister, and with or without priming of the valve, quality of active ingredient (including crystal form, if relevant), and particle size distribution by mass of the active ingredient (except in cases where the active ingredient is in solution at any stage of the finished product manufacturing process).

8.2. Physical equivalence

8.2.1. Measuring particle size distribution

Particle size distribution of the inhaled aerosol or powder can significantly affect deposition within the respiratory tract. It is important that the mass distribution rather than the number distribution of the aerosol particles be determined, and that the particles measured actually contain the medicine. Because of the non-uniformity of material distribution in poly-disperse droplets and particles which are physically and chemically heterogeneous, it is critical that the sizing method be able to distinguish the active substance from other components of the aerosol. The probability that any given aerosol droplet contains the active substance is dependent on the drug concentration and both droplet and drug particle size.

Light scattering or optical methods are unsuitable for pressurised aerosols as they are unable to distinguish between droplets containing drug and those containing only excipients, and do not give any information about the aerodynamic diameter of the particles. With the exception of microscopy they are, however, suitable for routine quality assurance of aerosols generated from solutions, or dry powder inhalers which contain no excipients, particularly where the diameter of particles is ≥ 2 micrometres.

The most direct method for determining particle size distribution is to fractionate the material by impaction using a multistage liquid impinger or a multistage cascade impactor, each with sufficient stages to enable the distribution to be defined adequately. The amount of drug substance in each fraction is then determined.

Instruments are commercially available which have been factory calibrated using mono-disperse aerosols at various flow rates.

Careful design of the input port of the inhaler device is required to take into account initial deposition of the aerosol in the mouth resulting from incomplete evaporation of the propellant, and to reduce the chances of overloading the first stage of a cascade impactor. The use of a large expansion chamber for the input port is not recommended as it would effectively act as a spacer. Input ports similar to those in Apparatus A or B of the BP are suitable.

In determining the particle size distribution of a product by cascade impaction, the number of actuations employed per replicate should be kept to a minimum to avoid the masking of variations, and should be consistent with the limit of sensitivity of the best available assay method.

If a manufacturer does not carry out the sizing under appropriate conditions or cannot provide a rational quantitative estimate of hygroscopic growth by an indirect method, then a justification should be provided as to why such data are not necessary.

If the mass of the particles is log-normally distributed, the mass median aerodynamic diameter and the geometric standard deviation of the particles give a good characterisation of the aerosol. The distribution pattern of two aerosols can then be compared statistically. The 90% confidence intervals for the ratio of the mass median aerodynamic diameters may also be a useful parameter for comparison of two products.

In cases where the particle size distribution of aerosols deviates significantly from log-normal, comparison of the respirable and non-respirable fractions may be more useful.

While the twin-impinger method for determining the particle size of pressurised aerosols (such as that adopted by the BP) is based on measurement of the drug mass aerodynamic diameter, it is limited in that only 2 fractions can be collected (particles above and below approximately 6.5 micrometres in the case of the BP). Therefore, a complete aerodynamic mass distribution cannot be defined.

It follows that the twin-impinger method is generally not useful for product development nor for comparison of multi-source and innovator metered dose aerosols, although it may be suitable for routine quality control of products. The twin impinger may also be acceptable for product development where a manufacturer has established an *in vitro* / *in vivo* correlation for the product in question.

Comparison of the particle size distributions of different products should be carried out under conditions which are clinically relevant. For example:

slow flow rates of 25-35 L.min⁻¹ are likely to reflect the 'worst possible' case of the effect of inspiration on de-aggregation of dry powders by patients unable to breathe at a faster rate

- ☞ dry powder inhalers generally produce smaller particle sizes at higher flow rates, and
- ☞ with propellant-driven generators, slow flow rates may produce unrealistically small particle sizes by allowing excessive time for evaporation of the propellants.

A rationale should be provided for whatever the flow rate and other test conditions are chosen, preferably reflecting *in vivo* data and/or clinical use.

8.2.2. Particle size

For corticosteroids and other medicines where side effects may follow oropharyngeal deposition, it is recommended that specifications be established for the:

- ☞ maximum amount of drug leaving the aerosol generator and likely to deposit in the oropharynx (aerodynamic diameter greater than approximately 4.7 micrometres); and
- ☞ amount likely to deposit predominantly at the desired sites (ie, the amount of drug contained in aerodynamic size fractions below approximately 4.7 micrometres).

The actual cut-off diameters may vary from one therapeutic class of medicine to another. This variability should be based on clinical evidence of optimum site of deposition. For example, for new beta-2 agonists the optimum mass particle size distribution is in the order of >40% below 3-4 micrometres aerodynamic diameter so as to ensure acceptable airways penetration.

8.3. Clinical Equivalence

The minimum requirement for establishing clinical equivalence is a comparison of clinical efficacy with the reference product, in a properly designed and conducted study of acceptable statistical power. The study should incorporate appropriate monitoring of adverse effects. Pharmacodynamic measurements should be incorporated in the protocol.

Applicants must provide certification that the study was carried out with Ethics Committee or Institutional Review Board approval, using appropriate codes of Good Clinical Research Practice.

Bronchoconstriction may occur in sensitive individuals during clinical studies comparing products which do not contain a bronchodilator. Therefore, all clinical studies involving products containing non-bronchodilator medicines should include measures to detect bronchoconstrictive responses.

Supporting clinical and physical (particle size distribution) data are required for spacer devices recommended for use with inhaled products. These data should be generated for each product recommended for use with each spacer device.

8.3.1. Statistical analysis

When conducting clinical trials to compare two similar metered dose inhalers (such as two bronchodilators) the confidence interval approach would be an appropriate form of statistical analysis. The procedure is outlined above in [Section 7.10](#).

In general, two products may be considered clinically equivalent if their relative effect does not differ by more than 20%, ie, if the confidence interval for the effect ratio of multi-source to reference product (calculated using log-transformed data) falls within the range 80-125%.

However, a confidence interval width of 80-125% may not always be appropriate for clinical studies for non-steroidal prophylactic products and glucocorticoids, due to the inherently greater variability in such studies. The applicant should justify any confidence interval falling beyond 80-125%.

8.3.2. β -Sympathomimetic medicines

The minimum requirement to establish the bioequivalence of a multi-source β -sympathomimetic product against the reference product is a comparison of:

- ☞ the bronchodilator effect, using the forced expiry volume in one second (FEV₁) and/or measurements of the area under the curve (AUC) for FEV₁ over time in mild to moderate asthmatics; and
- ☞ the broncho-protective effect, using controlled challenge tests such as a histamine provocation test.

Subjects participating in bronchodilation and broncho-protective effect studies should have reversible airflow obstruction. They should be stable asthmatics who have shown a bronchodilator response of at least 20%, and have been shown to be stable for at least 4 weeks prior to the study, that is, their levels of symptoms and medication should be constant and they should be free from viral infections. The stability of FEV₁ between study days should be assured (ie, $\pm 15\%$ or below is preferable) and there should be guidelines on the continuation or cessation of other medication. Slow release theophylline should be withheld for at least 24 hours prior to the study, and other inhaled bronchodilators for an adequate washout period. On the study day, subjects should be stable for half an hour before the study commences and medicine administration should be standardised.

Bronchodilation

A double blind placebo-controlled cross-over study should be conducted to compare 1, 2, and 4 puffs of reference product versus 2 puffs of the multi-source medicine versus 2 puffs of placebo in stable asthmatics to measure the maximum increase in FEV1 time course and duration of bronchodilation. Two puffs of the multi-source product should have significantly greater effect than 1 puff of reference product, and less effect than 4 puffs of reference product ($p < 0.05$). Two puffs of the reference and 2 puffs of the multi-source product should not be significantly different ($p > 0.05$).

Broncho-protective effects

A double blind placebo-controlled methacholine challenge cross-over study ($n=16$) should be conducted to compare 1, 2, and 4 puffs of reference product versus 2 puffs of multi-source product versus 2 puffs of placebo in stable asthmatics. The dose of methacholine required to induce a 20% fall in FEV1 of a patient pre-treated with β -agonist at the time of expected maximum effect should be measured and the time course and duration of the effect should be examined. The higher the challenge dose of methacholine required, the higher the protective effect of the beta-agonist.

The multi-source product must not produce a significantly worse cardiovascular response or a significantly greater incidence of adverse events than the reference product.

A spacer device could be used for the study if it is recommended that the device routinely be used with the product.

For multi-source β -sympathomimetics, it is accepted that two products are considered clinically equivalent if their relative effect does not differ by greater than 20%, ie, if the 90% confidence interval (calculated using log-transformed data) lies within the range 80-125% of the value for reference product. This range would also take into account the expected consistency of overall delivery of medicine from the product.

Study numbers should be based on power calculations to detect a difference if one really exists (eg, 90% power to detect a 20% difference at the 0.05 level).

AUC for FEV1 over time should usually be measured for a sufficient duration to define fully each response curve. Extrapolation to infinite time is not necessary. Provided the baseline is tightly controlled, it would be sufficient to base the comparisons on absolute values.

If no difference in efficacy is shown by the study, and the propellants and dispersing agents in the multi-source product are not new to aerosol formulations, then no further clinical studies should be required.

8.3.3. Anticholinergic medicines

The principles applying to establishing clinical equivalence of β -sympathomimetic medicines outlined above in [Section 8.3.2](#) also apply to applications for consent to distribute multi-source inhalers containing anticholinergic agents.

8.3.4. Non-steroidal prophylactic medicines

Applications for consent to distribute multi-source medicines used for the prophylactic treatment of asthma, by inhibition of the release from effector cells of mediators of the allergic reaction, should be supported by acute clinical studies (and sometimes, long term clinical studies) comparing efficacy against the reference product.

A comparison of their ability to protect against a challenge (such as cold air, exercise, or sulphur dioxide) may suffice. Providing this study shows equivalent performance, and the aerodynamic behaviour of the products is comparable, no further studies are required. However, if a difference in effect is shown by the acute study, long term comparison of clinical efficacy (such as improvement of spirometry or a reduction in the need for medication) or a study defining the *in-vivo* deposition profile of the multi-source inhaler in relation to the reference will be required.

As determination of pharmacodynamic effects for non-steroidal prophylactic medicines are inherently more variable than those for bronchodilators, appropriate allowance should be made in terms of discriminatory power and acceptable difference.

8.3.5. Glucocorticoids

For inhaled glucocorticoids, two methods can be used to establish clinical equivalence. These are described in guidance notes published by the [European Commission's Committee for Proprietary Medicinal Products](#) (CPMP) and [Health Canada](#).

The CPMP Note for Guidance: *Replacement of chlorofluorocarbons (CFCs) in metered dose inhalation products* gives the following advice and procedure for establishing equivalence of glucocorticosteroid inhalers:

“The demonstration of clinical bioequivalence of inhaled glucocorticosteroids is difficult and at this stage in our knowledge the only definitive efficacy studies are the parallel group “head-to-head” direct clinical comparisons, preferably in steroid-naive patients, with demonstration of clinical efficacy based on assessments made by the patient at home, recorded on diary cards, and made at regular, say 2 weekly, intervals in the clinic. Assessments would include pulmonary function measurements, symptoms scores, inhaled bronchodilator requirements and rate of exacerbations, defining beforehand an adequate primary outcome-variable. Studies should address a particular disease severity/dose regimen. The duration of treatment would need to be a minimum period of 4 weeks; longer treatment periods may be advantageous.

Since improvement in patients who are stabilised on corticosteroids is unlikely, the use of such patients is discouraged. However, if patients on corticosteroids must be entered into a trial, the pre-entry criteria, the expected improvements and the size and duration of the trial should be justified.

Single dose allergen challenge studies are artificial compared with natural exposure. There is a body of evidence which would support the use of the late response as a clinical model for the evaluation of potential new therapeutic agents, for early dose ranging in Phase II studies and the investigation of basic mechanisms of allergic asthma.

However, there is very little information on the reproducibility or dose-dependency of the late response and therefore its use in the demonstration of clinical bioequivalence is extremely limited and would not be appropriate.

Appropriate safety monitoring should be carried out, including some measure of systemic effect, eg, assessment of hypothalamic adrenocortical function and assessment of paradoxical bronchospasm.”

The Canadian *Draft guidelines on in vivo criteria to establish equivalence of safety and efficacy of a multi-source or second entry drug delivered by metered dose inhaler for drugs intended for delivery to the lower respiratory tract*, published by the Health Product and Food Branch of Health Canada describe a different approach where dose back-titration is used to determine if the minimum effective dose is the same for the reference and test product. The products are compared in a double blind parallel-group comparison in asthmatic patients already controlled on inhaled steroid (eg, a minimum of 800µg beclomethasone per day). The daily dose of steroid is reduced in a stepwise manner (eg, by 200µg/dose each week) until patients have an exacerbation of their asthma. The exacerbation is treated by resuming twice the previous minimum dose of steroid. There must be no statistically significant difference in the dose of inhaled steroids between the reference and test product at the time of exacerbation in the two groups.

Study numbers should be based on power calculations to detect a difference if one already exists (eg, 90% power to detect a 20% difference at the $\alpha = 0.05$ significance level). Adverse effects such as dysphonia, thrush, adrenal suppression should be monitored in these clinical studies.

8.4. Powders for Inhalers

Where a new medicine is essentially the same as a product already on the market, an abridged application should be submitted. Where the two products are not essentially the same, a New Medicine Application including clinical safety and efficacy studies is required. The principles applying to determination of equivalence for pressurised inhalers, in terms of clinical requirements, are applicable to powders for inhalation.

As the delivery device can significantly alter the deposition profile of an inhaled powder, changes in the device can result in the modified system being regarded as a new product. Comparative efficacy data are then required. Major changes in the formulation of the inhaled powder itself must also be accompanied by comparative efficacy data, as the deposition profile may again be affected (see [Section 8.3](#) for details).

For a minor change in the powder component of an already approved product, the medicine mass aerodynamic properties of the two formulations should be defined. If the two formulations display similar performances *in vitro*, no further studies will normally be required.

However, if a difference is observed, clinical data to confirm equivalence or a justification as to why such data are not required, should be provided.

8.5. Nasal Inhalation Products

Nasal inhalations, administered for a local effect, should have a particle size distribution appropriate for nasal application, ie, particles are greater than 20 micron aerodynamic diameter or the deposition data show that >90% of particles are deposited in the nose.

Nasal inhalation intended to be absorbed and produce a systemic effect should be supported by *in vivo* bioavailability data as outlined in [Part D, Section 7](#) (Bioequivalence Testing of Oral Medicines).

8.6. Changes to Currently Marketed Products

Sponsors may propose changes to inhaled products with consent to distribute in New Zealand. The change may be *major* (such as valve size or design of the inhaler) or *minor* (such as a change in the content of propellant which has minimal effect on the partial pressure of the mixture). Providing the change is relatively minor, physicochemical methods such as measurement of drug mass aerodynamic particle size distribution of the changed and current products will normally be sufficient to establish equivalence of performance. However, if a difference in physical performance is found, or if the proposed change is likely to cause a difference in particle size distribution or clinical effect, either a clinical study or a justification as to why this is unnecessary should be provided.

8.6.1. Rubber or plastic components

Any notification to a product which involves, or is likely to affect, rubber or plastic components should include data establishing whether or not leaching occurs. If leaching occurs, the identity and quantities of the leached substances should be established and comment provided on their toxicological and clinical implications.

8.6.2. Replacement of chlorofluorocarbons

As the production and use of chlorofluorocarbons (CFCs) is being phased out internationally, many companies are replacing these propellants with non-CFCs. The European Commission has produced the guideline *Replacement of Chlorofluorocarbons (CFCs) in Metered Dose Inhalation Products* ([CPMP Guideline III/5378/93](#)). Applicants who wish to replace existing chlorofluorocarbons with alternative propellants should follow this guideline.

8.6.3. Changes to powders for inhalation

As the delivery device can have a significant influence on the deposition profile of an inhaled powder, any modification to its design or method of operation usually means the modified product is a new product and thus requires full clinical as well as physicochemical data. Similarly, a substantial change in the formulation of the inhaled powder, such as addition of an agent to modify its flow or hygroscopic properties or the removal or substitution of carrier, will necessitate the same data because the deposition profile could change markedly.

Physical measurements, such as drug mass aerodynamic particle size distribution of the delivered aerosol, are usually sufficient to support minor changes in the content of an excipient in an already approved powder for inhalation or minor changes to the delivery device. These data should be generated at several flow rates. However, if significant physical differences are observed, either clinical data or a justification as to why such data are unnecessary should be submitted.

Any comparative efficacy study performed to support a change to a powder for inhalation should encompass the principles for establishing clinical equivalence of inhaled products as outlined above.

Section 9: Guidance on analytical procedure validation

9.1. Introduction

The information that follows is guidance to industry on Medsafe's expectations with reference to analytical procedure validation. Departure from this guidance is permissible if sufficient justification is provided. Equally, Medsafe may request additional information if it has concerns over an aspect of an analytical procedure's use.

This guidance covers three topics, which address Medsafe's expectations regarding:

- the validation of pharmacopoeial methods
- the validation of non-pharmacopoeial methods
- the conduct of analytical procedure transfer.

In addition, each section includes Medsafe's data requirements as they pertain to the submission of a New Medicine Application (NMA) or Changed Medicine Notification (CMN).

9.2. General

Medsafe expects all analytical procedures, (pharmacopoeial, and non-pharmacopoeial) to have been verified as suitable for use at each site where testing is to occur. It also expects that method verification will have occurred before use. This expectation applies to analytical procedures used to test both non-prescription medicines and prescription medicines.

The extent of verification required is determined by:

- whether the analytical procedure is in a recognised pharmacopoeia
- the type and complexity of the analytical procedure in question.

Verification encompasses a range of techniques including: full validation in accordance with ICH guidance, analytical procedure transfer validation, or conformance with system suitability criteria.

9.3. Validation requirements for pharmacopoeial analytical procedures

Medsafe expects pharmacopoeial analytical procedures to be verified as suitable for use at all sites of testing. In most cases this means conformance with system suitability criteria and does not involve full validation in accordance with ICH guidance. Notable exceptions to this rule are:

- a) *Finished product assay procedures.* Evidence is required that the drug product excipients do not interfere with the procedure.
- b) *Impurity (in the active ingredient) analytical procedures.* Evidence of appropriate validation will be required where the active ingredient is made using a different route of synthesis from the route that underpins the pharmacopoeial monograph, or where a non-pharmacopoeial impurity is specified.

- c) *Biological tests eg, microbial quality, sterility, endotoxins.* Such tests require preparatory investigations to have been undertaken to ensure the analytical procedure is functioning correctly and is suitable for use. Evidence of this is required.

New Medicine Application and Changed Medicine Notification Requirements

- For standard pharmacopoeial analytical procedures, other than those specified above, no validation or analytical procedure transfer data is required to be submitted for sites of testing.
- For non-standard pharmacopoeial analytical procedures, such as those specified above, validation reports are required from the site of analytical procedure development, but not from each proposed site of testing.

9.4. Validation requirements for non-pharmacopoeial analytical procedures.

Medsafe expects non-pharmacopoeial analytical procedures to be validated in line with ICH guidance at the site of analytical procedure development.

Non-pharmacopoeial analytical procedures should be verified as suitable for use at all nominated sites of testing, either through a revalidation process that is in-line with ICH guidance, or through use of an analytical procedure transfer process (discussed in more detail below).

New Medicine Application and Changed Medicine Notification Requirements

- For a non-pharmacopoeial analytical procedure a validation report is required from the site of analytical procedure development.
- A revalidation report or evidence of analytical transfer (see 5. Analytical Procedure Transfer) is required for each additional site of testing.

9.5. Analytical Procedure Transfer

Analytical procedure transfer is the process that qualifies a laboratory to use a particular analytical procedure that has been developed in another laboratory.

It is important that the analytical procedure is validated and approved at the Sending site and that the Receiving site has recent and current evidence of GMP. Appropriate accreditation such as ISO 17025 may be considered as an alternative to GMP evidence on a case by case basis.

The technical requirements of the transfer process may vary depending on the type of analytical procedure, the nature of company arrangements and laboratory standard operating procedures.

Fundamentally, analytical procedure transfer comprises repeated testing of common samples at the Sending and Receiving sites in order that comparative analysis may be undertaken.

Useful reference texts on the technical requirements for analytical procedure transfer are:

J. Ermer, J. and Miller, J.H.McB (Eds). 2005. *Method Validation in Pharmaceutical Analysis. A guide to Best Practice*. WILEY-VCH Verlag GmbH & Co KGaA, Weinheim. ISBN 978-3-527-31255-9.

ISPE. 2003. *ISPE Good Practice Guide: Technology Transfer*. ISPE. www.ispe.org. ISBN 1-931879-13-3

New Medicine Application and Changed Medicine Notification Requirements

- Evidence of analytical procedure transfer should be provided for all sites of testing for which analytical procedure revalidation has not occurred.
- Evidence of analytical procedure transfer should preferably be in the form of a report and be accompanied by a justification for the extent of the analytical procedure transfer undertaken.

NOTE: Medsafe's objective in requesting this information is to enable an informed assessment of the proposed testing site's capabilities. Where it is not clear that the analytical procedure has been suitably verified, further questions may be asked of the applicant.

