

Appendix 8 Data Requirements for New Medicine Applications and Changed Medicine Notifications

Section 1: 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.

1.1. Standard Requirements for New Medicines

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

1.1.1. 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) must relate to the product (or product class) and activity concerned, (b) must be issued by authorities recognised by Medsafe, and (c) must not be due to expire by the time the product is likely to be approved for distribution in New Zealand.

For prescription medicines 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 generic prescription 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.

1.1.2. 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 been 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). 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)

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

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 must have been justified and shown to yield finished product of equivalent quality.

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

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 nonpharmacopoeial 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

Refer to Part 6 of the Guidelines for the Regulation of Therapeutic Products in New Zealand.

1.2. Additional Data Requirements for Abbreviated applications

1.2.1. 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 packaging¹.
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.

¹ The product must comply with Medsafe's current labelling requirements.

1.3. 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 [EMA](#) and [FDA](#) Internet web sites and may be downloaded from there (see Subsections [1.3.2](#) and [1.3.3](#) 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 (<25degC) than in Australia (<30degC).

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).

1.3.1. 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".

1.3.2. 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>

1.3.3. 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>

1.4. 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: 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

2.1. 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.

2.1.1. 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 2.2](#) 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.

2.1.2. 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.

2.2. 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.

2.3. 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 contaminating 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.

2.4. 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 3: Guidance on analytical procedure validation

3.1. 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).

3.2. 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.

3.3. 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.
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- 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.

3.4. 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.

3.5. 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 978-3-52731255-9.

ISPE. 2003. *ISPE Good Practice Guide: Technology Transfer*. ISPE. www.ispe.org. ISBN 1931879-13-3

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.

Section 4: 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: 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.

5.1 Standard Requirements for CMNs or CRPNs

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
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- 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 Other	3% 1%
Binder	0.5%
Lubricant: Calcium stearate Magnesium stearate Other	0.25% 0.25% 1%
Glidant: Talc Other	1% 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 GRTPNZ Part 4) 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 GRTPNZ Part 4).

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.

5.2 Self-assessable Changes

As indicated on the CMN application form, some changes are self-assessable.

Except in the case of a changed label, updated specifications or data sheet, no supporting 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.

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.

One copy of the CMN or CRPN form should be submitted for a material change that is self-assessable, along with supporting documents (eg. updated specifications, in-process controls, or other documentation described below).

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 (eg. those issued by international organisations such as the WHO and NIBSC, or those approved as primary standards as part of the NMA for the product); 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 relevant data and CoAs, 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.

Changes to reference standard shelf lives/expiry/retest dates

Where a protocol for the retest/expiry date of a reference standard has been previously approved (via NMA or CMN), then a SACN (**Shelf life/storage conditions – Reference Standard – Grade 2**) may be used to extend the shelf life/expiry/retest date. Relevant data/CoAs should be included with the submission, along with an assurance that no other changes are made, and that Medsafe will be advised immediately of any aberrant results that arise during routine use of the standard. If a relevant protocol has not been approved, then the extension should be submitted as a CMN (**Shelf life/storage conditions - Reference standard – Grade 1**), along with appropriate data. A protocol for subsequent use of SACNs may be included with the submission.
