MEDSAFE

New Zealand Medicines and Medical Devices Safety Authority

Guideline on the Regulation of Therapeutic Products in New Zealand

Ingredients in New Medicines and Related Products

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Contents

1. Active Pharmaceutical Ingredients

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 API are usually described in a '**Drug Master File**' (DMF) submitted to the regulatory authority by the manufacturer of the API.

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

For biological and biotechnological products, information on the production, quality control, and stability of the API is usually submitted in a complete section 3.2.S that is provided as part of the dossier for the finished product.

1.1 Drug Master File (DMF)

To refer to the DMF in an application, the applicant must have the written permission of the API manufacturer who submitted the DMF. A "letter of access" from the API manufacturer that is addressed to Medsafe and clearly states the New Zealand sponsor and finished products to which it applies, must be sent to Medsafe either with the DMF or separately.

If an API manufacturer has supplied (or been asked to supply) a DMF to Medsafe as part of a New Medicine Application (NMA) for a medicine or related product, it is not necessary for a further copy of the DMF (or part thereof) to be provided for an NMA for another product sponsored by a different sponsor. However, the API manufacturer needs to provide Medsafe with a new letter of access, referring to the previously supplied DMF and the new sponsor and associated finished products.

New Zealand 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 API manufacturer and the New Zealand sponsor that ensures the sponsor and Medsafe are informed of any significant change made to the method of manufacture or specifications of an API, before it is implemented.

Quality control of the bulk API is carried out by both the manufacturer of the API and by the manufacturer of the finished product. Testing by the manufacturer of the bulk API is usually described in a DMF. Good Manufacturing Practice requires the finished product manufacturer to re-test the API's identity, potency, and purity before use in the manufacture of finished products. Additional testing may be required depending on the finished product dose form that the API is used in. This testing should be described in the dossier for the finished product.

DMFs should be updated periodically to reflect any changes. New Zealand sponsors 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 need to be described in sufficient detail to enable Medsafe to determine if any changes have been made to the characteristics, manufacture or quality control of the API concerned and what those changes are. Where Medsafe evaluation of the changes is required, the sponsor will be required to submit a Changed Medicine Notification (CMN) and pay the appropriate fee.

When a DMF is not required

A DMF is **not** required for:

- any API that is controlled according to a relevant monograph in the European Pharmacopoeia and for which a valid (recently issued) European Pharmacopoeial Commission "Certificate of Suitability" (CEP) is provided (see section 1.3 below for details)
- any API predominantly used in a lower-risk medicine (eg, paracetamol) or related product. If the API is also used in a higher- or intermediate risk medicine, a DMF or a European Pharmacopoeial Commission CEP may be required to support an NMA or Changed Medicine Notification/Changed Related Product Notification (CMN/CRPN) relating to that product.
- common inorganic substances and simple organic compounds available in high purity from commercial suppliers, 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 APIs, evidence needs to be submitted by the finished product manufacturer that the API(s) 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 API.

1.2 Format for a DMF

DMFs compiled using the Common Technical Document (CTD) format or older European or United States (US) formats 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 API manufacturer, a copy of the full report should be forwarded to Medsafe with the DMF. If the report is not available, the API 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 product manufacturer and the second (closed) section containing information not accessible to the finished product manufacturer.

1.3 Certificate of Suitability

Where an API 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 CEP. The CEP confirms that the purity of the API, as produced by the API manufacturer, is suitably controlled by the monograph in the European Pharmacopoeia. The CEP may then be submitted in lieu of a DMF, removing the need for regulatory authorities to carry out their own detailed assessment of the data. For details of the certification scheme, contact the secretariat of the European Pharmacopoeial Commission. Some information is available on the internet site: http://www.pheur.org.

Where a European Pharmacopoeial Commission CEP is submitted in lieu of a DMF, the New Zealand sponsor must also provide a written assurance that any conditions attached to the CEP 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 API batch used in product intended for the New Zealand market.

The European Pharmacopoeial Commission also assesses and issues CEPs for substances used as APIs or excipients in pharmaceutical products to confirm that they comply with European Pharmacopoeial requirements for minimising the risk of transmission of animal spongiform encephalopathies. Medsafe accepts these CEPs.

Where a European Pharmacopoeial Commission CEP is submitted in lieu of a DMF, the applicant for an NMA or CMN/CRPN must ensure that the CEP is submitted with the written permission of the API manufacturer. Submission of the CEP as part of the dossier of data supporting an NMA or CMN/CRPN implies, but does not prove, that there is a commercial agreement between the applicant and the API manufacturer. This agreement between the parties must be confirmed to Medsafe by means of a formal “letter of access” from the API 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 API manufacturer will, if requested, supply directly to Medsafe data relating to the manufacture, quality control and stability of the substance concerned.

2. Ingredients of Human or Animal Origin

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 below should be followed in preparing the documentation to provide this evidence.

An European Pharmacopoeial Commission CEP is acceptable as evidence of freedom from TSE agents.

Products containing APIs or excipients manufactured from human plasma require supporting information to provide assurance of the suitability of the plasma. This documentation is referred to as Plasma Master File (PMF). For guidance regarding the content of the PMF, refer to EMEA/CHMP/BWP/3794/03 Rev.1, and EMA/CHMP/BWP/706271/2010. PMFs should be updated at least annually as described in section 11 of the Changed Medicine Notifications and Non-notifiable Changes guideline.

***Guidelines relevant to this section*:**

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines:

- ICH Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
- ICH Q5A(R1) and ICH Q5A(R2) EWG Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin
- ICH Q5D Quality of Biotechnological Products: Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products

Committee for Proprietary Medicinal Products (CPMP) Guidelines and position papers:

- Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 Rev. 3)
- Guideline on the investigation of manufacturing processes for plasma-derived medicinal products with regard to vCJD risk (CPMP/BWP/CPMP/5136/03)
- Position Paper on Production of Tallow Derivatives for Use in Pharmaceuticals (CPMP/1163/97)
- Guideline on plasma-derived medicinal products (EMA/CHMP/BWP/706271/2010)
- Guideline on the Scientific Data Requirements for a Plasma Master File (PMF) Revision 1 (EMEA/CHMP/BWP/3794/03 Rev.1)
- Guideline on the use of bovine serum in the manufacture of human biological medicinal products (EMA/CHMP/BWP/457920/2012 rev 1)
- Guideline on the use of porcine trypsin used in the manufacture of human biological medicinal products (EMA/CHMP/BWP/814397/2011)
- Guideline on the adventitious agent safety of urine-derived medicinal products (EMA/CHMP/BWP/126802/2012)
- Note for Guidance on Virus Validation Studies: The Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses (CPMP/BWP/268/95)

Food and Drug Administration (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

3. Colouring Agents

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

https://www.medsafe.govt.nz/regulatory/guideline/PermittedColourings.asp

4. 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.

4.1 Registration of a Proprietary Ingredient with the database

The New Zealand Medicines Act 1981 requires 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 a 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's 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 Australian Registry of Therapeutic Goods (ARTG) number from Australia's Therapeutic Goods Administration (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 should be submitted electronically to medsafeapplications@health.govt.nz.

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.

4.2 Proprietary Ingredient form

The Proprietary Ingredient form has been developed to act as an 'audit trail' between companies that market consented 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.

4.3 Registration search

Proprietary Ingredients can be checked for registration by searching the 'ingredient field' in the Medsafe Product/Application Search database, found 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 Search 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.

Document history

Revision Date	Version Number	Summary of Changes
January 2023	New	New document following major review and restructure of GRTPNZ Part 2, which has been obsoleted.