



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Regulatory Guidelines for Prescription Medicines



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APPENDIX 11: DRUG MASTER FILES AND CERTIFICATES OF SUITABILITY

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A. Drug Master Files for Drug Substances used in Medicines

Where a drug substance used in the manufacture of a medicine is sourced from a third party manufacturer, data on its manufacture, quality control and stability may be submitted via a Drug Master File (DMF). The relevant European guidelines for the European Drug Master File Procedure, which has been adopted by the Therapeutic Goods Administration (TGA), are available from the TGA web site¹.

A DMF using the United States format is acceptable if a DMF formatted according to the Common Technical Document (CTD) or the older European format is not available.

Where the drug substance and drug product are manufactured by the same company, information on the production, quality control and stability of the drug substance may be submitted as part of the dossier for the drug product rather than in a separate DMF. However, the company is not precluded from submitting a DMF for the drug substance if it prefers to do so.

Note that, where a DMF is to be submitted in support of an application for approval of a new finished medicinal product or a change to a registered product, the DMF needs to be received by the TGA before the application can be accepted for assessment.

In order to refer to a DMF in an application, the drug product sponsor must have the written permission of the drug substance manufacturer who submitted the DMF. A *letter of access* from the drug substance manufacturer, addressed to the TGA, indicating clearly the product sponsor to which it applies and providing certain other information and assurances required by the TGA, should be sent directly to the TGA, either with the DMF or separately.

A proforma for letters of access to DMFs is available as part of Module 1 of the CTD^{2,3}. This proforma must be used rather than that used in Europe.

Drug product sponsors are responsible for the quality of their products and the raw materials used to manufacture them. By completion of the relevant section of the Application proforma, a sponsor provides written assurance that there is a formal agreement between the active pharmaceutical ingredient manufacturer and the sponsor designed to ensure that information will be communicated by the manufacturer to the sponsor and the TGA before any significant change is made to the drug substance. Such variations may include changes to the method of manufacture, test methods and specifications of the drug substance.

Where the product sponsor is not also the product manufacturer and its contract agreement is with the product manufacturer only rather than with the drug substance

¹ http://www.tga.gov.au/docs/html/euguide/euad_qual.htm#qualitygeneral

² <http://www.tga.gov.au/docs/html/eugctd.htm>

³ Note that, the Forms 6A and 6B in the earlier version of these guidelines are no longer required. Instead, the assurances in these forms are included in the proforma for the letter of access and the Application proforma available in Module 1 of the CTD.

manufacturer, completion of the relevant section of the Application proforma is still necessary, since the sponsor has an obligation under the Act to ensure that no changes are made to the product, including the drug substance, without its knowledge and TGA approval (if required).

DMFs should be updated periodically to reflect any changes. The drug product 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 the TGA before implementation. It is the sponsor's responsibility to judge whether the proposed changes require prior assessment and approval by the TGA or may be implemented through self-assessment in accordance with the Self-Assessable Change guidelines (see Appendices 12 and 13).

A DMF is not required for common inorganic salts (for example, sodium chloride, and other common electrolytes) used and regarded as drug substances in products such as injections and dialysis solutions, and simple organic compounds available commercially in high purity (for example, naturally occurring organic acids and their salts, including ascorbic acid and sodium citrate, and simple mono- and disaccharides such as glucose and sucrose). 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 by the TGA to determine their appropriateness and adequacy to ensure the quality of the substance.

Where a DMF is submitted for a drug substance controlled according to a pharmacopoeial monograph, the DMF should include a discussion of the potential impurities most likely to arise during synthesis using the actual manufacturing process described in the DMF together with evidence that these impurities are adequately controlled by the test procedures described in the pharmacopoeial monograph. Where particular impurities found in the substance are not listed in the monograph but are proposed to be allowed at levels above the Committee for Medicinal Products for Human Use (CHMP)/International Congress on Harmonisation (ICH) limits for qualification, a justification (including toxicological data, if appropriate) should be provided.

B. Data to be Supplied in DMFs for Antibiotics Produced by Fermentation (wholly or in part)

These guidelines have been developed to assist the sponsor regarding the type of Drug Master File information that should be provided (in addition to that detailed above in Part A) to give the evaluator an overview of the key stages of the fermentation process. Fermentation processes, because of their biological nature, are prone to produce unwanted and sometimes unexpected compounds unless conditions are carefully and strictly controlled. The evaluator's primary concern is to assess whether the process at given site(s) is capable of consistently yielding active raw material of desired character and quality.

The following points elaborate in detail items related to the manufacture and stability of drug substances produced by fermentation covered in EU guidelines adopted in Australia⁴.

1. Plant/site(s) information

Provide:

- the full address(es) of all plants involved with the manufacture of the fermentation product;
- evidence that each of the nominated plants meets a satisfactory standard of GMP.

2. Fermentation plant description

Provide a description of the fermentation plant, including details of the number, type, and capacity of the pre-fermenters, batch fermenters, and recovery equipment.

3. Plant dedication

Provide a statement as to whether or not the full capacity of the plant is dedicated to the production of a particular substance. If not, then details should be provided of:

- other substances produced, (and the monitors employed to detect them);
- whether or not dedicated equipment is used;
- whether or not production activities are segregated;
- whether or not campaign production occurs;
- clean-up procedures to eliminate cross-contamination by the other substances.

4. Producer strain of microorganism

Provide full details of the strain of microorganism used in the fermentation process, including identification, source, strain improvement procedures, purity and stability

⁴ <http://www.tga.gov.au/docs/html/euguideh.htm>

checks, cell banking arrangements and storage, propagation, seeding procedures and whether or not it has been deposited in a recognised culture collection.

5. Fermentation media materials

Provide information concerning the materials used for the fermentation media. This should include raw material specifications, and how the media are sterilised prior to use. Where alternative nutrient sources are likely to be used, these should be itemised and specifications supplied. When precursors or inducers are used, their specifications should also be provided

Information should also be provided about the identity and source of any animal-derived materials used in the fermentation media, and how the risk of transmission of transmissible spongiform encephalopathies (TSE) is controlled.

6. Fermentation process

Provide a full description of the fermentation process, including conditions and controls, accompanied by a flow diagram. Include:

- details of all process controls and sampling procedures used to monitor for microbial contamination and to ensure that the fermentation process is proceeding satisfactorily;
- steps taken to monitor the process to ensure that the nominal factorial profile is likely to be achieved.

7. Isolation and purification procedures

Provide a full description of the isolation and purification procedures accompanied by a flow chart diagram:

- give details of all solvents and/or reagents used for each step and the percent purity of the product after each step;
- indicate if recycled solvents are used and provide details.

8. Additional recovery/reprocessing steps

Clearly state the procedures to be followed where additional recovery or reprocessing steps are required, or in the event of batch failure.

9. Drug substance quality control

Give a full description of active raw material quality control including tests used for the identification of the purified fermentation product, as well as how the potency or content of active ingredient in the drug substance is determined and quantified, as follows:

- where a microbiological assay is used, it should be supported, whenever possible, by some more specific analytical method such as HPLC. This is

- particularly important in the case of those drugs, drug precursors or antibiotics with a factorial composition;
- the information required to characterise the ferment product should be comparable in extent and details to that of a totally synthetic drug substance and should include information on particle size, polymorphic forms, solvent status etc. (See CHMP guideline *Chemistry of Active Ingredients*⁵);
 - the factorial content should be clearly defined. Where a Pharmacopoeial monograph (for example, British Pharmacopoeia) exists for a factorial type antibiotic, then the factorial composition of the active raw material should reflect the monograph requirements. If the antibiotic from the ferment is found to possess a factorial composition significantly different from that expected, additional evidence as to the safety and the efficacy of this material may be required.

10. Impurities

Details of impurities (in-process and degradation) and their levels in the finished fermentation product should be defined and their limits justified. Where there is a significant difference in the impurity profile from that which has previously been established, the effect this may have on the safety of this material may need to be evaluated.

11. Batch to batch variation

In order to assess batch to batch variation, provide details of:

- quality of recent batches in the form of certificates of analyses;
- recent fermentation yield results and typical batch sizes;
- where the output from several fermenters is combined to constitute a blended batch of the finished fermentation product, details should be given.

12. Stability test data

Stability test data should be provided for at least 3 production batches and should include:

- batch details (batch number, date of manufacture);
- the general test methodology (duration of study, storage conditions of temperature and humidity, time points when samples were removed for analysis etc.);
- the analytical test methods (assay method of quantitation, determination of degradation products, moisture etc);
- validation of test methods;
- results of tests;
- conclusions.

⁵ <http://www.tga.gov.au/docs/pdf/euguide/vol3a/3aq5aen.pdf>

C. Certificates of Suitability of Monographs of the European Pharmacopoeia

Where a Certificate of Suitability (CEP) of Monographs of the European Pharmacopoeia is provided in lieu of a DMF for a drug substance that is the subject of a monograph in the European Pharmacopoeia (Ph. Eur.), the following must also be submitted concurrently:

- written authorisation from the drug substance manufacturer for the TGA to refer to the CEP (see below);
- a written assurance that no significant changes have been made to the manufacturing method since the certificate (or its last revision) was issued by the European Directorate for the Quality of Medicines (EDQM);
- a written assurance that any conditions/additional tests attached to the CEP by the EDQM and any tests and limits additional to those in the Ph. Eur. monograph (for example, particle size distribution, specific polymorphic form) required for the intended use of the substance will be applied to each batch of the drug substance destined for the Australian market;
- certificates of analysis (or equivalent analytical data) for at least 3 production scale batches demonstrating compliance with the monograph, any additional tests/limits attached to the CEP and any agreed additional tests/limits for the drug substance concerned;
- an outline of the route of synthesis (or manufacturing process).

In the case of a drug substance (for example, antibiotic) manufactured using fermentation, all the following additional information should also be provided:

- the identity of the producer organism(s);
- the identity and source of any animal-derived materials used in the fermentation media, and information about how the risk of transmission of TSE is controlled;
- a clear statement of the procedures followed in the event of batch failure or where additional recovery or reprocessing steps are required;
- a statement as to whether or not the full capacity of the plant is dedicated to the production of a particular substance. If not, then details should be provided of:
 - other substances produced, (and the monitors employed to detect them);
 - whether or not dedicated equipment is used;
 - whether or not production activities are segregated;
 - whether or not campaign production occurs;
 - clean-up procedures to eliminate cross-contamination by the other substances.

In order to refer to the CEP in an application, the product sponsor must have the written permission of the drug substance manufacturer. This permission should be in the form of a *letter of access* from the drug substance manufacturer, addressed to the TGA and indicating clearly the product sponsor to which it applies, including

certain other required information and assurances, and sent directly to the TGA, either with the CEP or separately (see Module 1: Administrative Information and Prescribing Information for Australia⁶).

A proforma for letters of access to CEPs is available in Module 1.4.3 of the CTD. This proforma includes specific assurances required by the TGA, and should be used rather than that required by European regulatory authorities.

The TGA may request additional information about the manufacture and quality control of the drug substance and/or how the impurity limits specified in the CEP have been justified by the manufacturer and assessed by the EDQM. The TGA may also request a copy of the EDQM Evaluation Report Parts A and B.

Where such a request is made, it is the responsibility of the sponsor to pass the request on to the EDQM and authorise it to send a copy of the reports direct to the TGA marked for the attention of the S31 Officer.

The acceptance of a CEP in lieu of a DMF for a drug substance does not remove the requirement for a finished product sponsor to notify the TGA of, or seek prior approval for, any changes made to that drug substance subsequent to the issue of the CEP. Amendments to the CEP that are allowed by the EDQM are not automatically accepted in Australia. However, an amended CEP can be submitted in support of an application to make changes to a drug substance.

⁶ <http://www.tga.gov.au/docs/pdf/euguide/tgamod1.pdf>