Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Guidance 11: Drug Master Files and Certificates of Suitability of a Monograph of the European Pharmacopoeia for drug substances

Version 1.0, August 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

Version history

Version	Description of change	Author	Effective date
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Contents

Introduction

This guidance is intended for manufacturers of drug substances for prescription medicines, and sponsors of prescription medicines sourcing drug substances from a third party manufacturer.

11.1 Drug Master Files and certificates of suitability

11.1.1 For drug substance sourced from a third party manufacturer

There are two mechanisms by which a sponsor can provide information about a drug substance sourced from a third-party manufacturer:

- a DMF or
- a CEP issued by the European Directorate for the Quality of Medicines & HealthCare (EDQM).

11.1.2 For ingredients of animal or human origin

A CEP does not contain sufficient information and will not alone be accepted.

Related information and guidance

- Therapeutic goods that contain or are produced from human blood or plasma
- Adventitious agent safety of medicines

11.2 What substances require a Drug Master File

A DMF is required for all drug substances that are sourced from a third-party manufacturer, except for the following substances:

- common inorganic salts that are used and regarded as drug substances in products such as:
  - injections
  - dialysis solutions (e.g. sodium chloride and other common electrolytes)
- simple organic compounds that are commercially available in high purity e.g. naturally occurring organic acids and their salts, including:
  - ascorbic acid
  - sodium citrate
  - simple monosaccharides
  - disaccharides, such as glucose and sucrose
- when a CEP has been provided in lieu of a DMF.

However, sponsors should include information (e.g. a certificate of analysis) to demonstrate that any common inorganic salts or simple organic compounds used as drug substances:

- are obtained from a reliable source
- consistently comply with applicable pharmacopoeial or nonpharmacopoeial specifications.

Note

- Any nonpharmacopoeial specifications need to be assessed by the TGA to determine their appropriateness and adequacy to ensure the quality of the substance.
- The evaluation of an application will not commence until the TGA receives the DMF.
- Mention the specific version number of the DMF in the application.

For a drug substance and drug product manufactured by the same company, include information on the production, quality control and stability of the drug substance as either:

- part of the application for the drug product, or
- in a separate DMF.

11.2.1 Acceptable format for Drug Master Files

Guidance for sponsors

The preferred format for DMF is the European Common Technical Document (CTD) format or the European format. However if the manufacturer has not used either of these formats, the TGA will accept a drug master file in the United States format.

Related information and guidance

- Guideline on active substance master file procedure (CPMP/QWP/227/02 Rev 1), adopted with annotation.

11.2.2 Letters of access to Drug Master Files

Guidance for sponsors

A Proforma *Letter of Access to DMF* is available in Module 1.6.3 of the CTD.

- Obtain written permission (i.e. a *Letter of Access*) from of the DMF owner to enable the TGA to access the current version of the DMF.

Request the manufacturer to:

- use the proforma in Module1.6.3 of the CTD prepare the *Letter of Access to DMF*
- clearly identify the sponsor the letter relates to

- provide information and assurances required by the TGA in Module 1.6 of the CTD
- send the letter directly to the TGA, either with the DMF or separately.

Note

- The proforma for *Letters of Access* used in Europe is not acceptable.

11.3 Sponsor's obligations regarding Drug Master Files

Sponsors:

- have an obligation under the standard conditions of registration, imposed under s. 28(3) of the *Therapeutic Goods Act 1989* (the Act), to ensure no changes are made to the product, including the drug substance, without their knowledge and TGA approval (if required).
- need a formal agreement with the manufacturer of the drug substance that ensures they will be notified before any changes are made to the drug substance.
- are responsible for determining whether:
  - the proposed changes require data to be submitted to the TGA
  - the variation can be made as a self-assessable request.

11.3.1 Updating drug master files

DMFs should be updated periodically to reflect any changes, and ensure that one of the following is forwarded to the TGA before the changes are implemented:

- the updated DMF (together with a detailed list of changes made), or
- details of any changes made.

Related information and guidance

- Minor variations to registered prescription medicines: Chemical entities
- Minor variations to registered prescription medicines: Biological medicines

11.4 Additional information in Drug Master Files for some drug substances: guidance for manufacturers

The TGA has adopted the European Medicines Agency (EMA) Guideline on active substance master file procedure (CPMP/QWP/227/02 Rev 1), adopted with annotation. In addition to the

requirements of the above EMA guideline; further information is required in the DMF for the following types of drug substances:

- drug substances with a default standard monograph
- sterile drug substances
- products of human or animal origin
- substances produced wholly or in part by fermentation

11.4.1 Drug substances with a default standard monograph

For drug substances that are the subject of a pharmacopoeial monograph in a default standard (British Pharmacopoeia [BP], European Pharmacopoeia [Ph. Eur.] or United States Pharmacopeia–National Formulary [USP–NF]):

Include the following in the DMF:

- a discussion of the potential impurities that are most likely to arise during synthesis using the manufacturing process described in the DMF
- evidence that these impurities are adequately controlled by the test procedures described in the pharmacopoeial monograph.

Alternative test procedures may be used if it can be demonstrated that both:

- the results obtained are equivalent to, or more stringent than, the pharmacopoeial requirements, and
- the method has been appropriately validated.

Provide justification (including toxicological data, if appropriate) if:

- impurities in the drug 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.

11.4.2 What to include in a Drug Master File for sterile drug substances

For drug substances (and/or excipients) that are terminally sterilised and do not undergo further sterilisation during manufacture of the drug product, ensure the DMF includes:

- information on bioburden
- details of physical and microbiological validation that show a sterility assurance level (SAL) of 10^{-6}.

For drug substances (and/or excipients) that are aseptically manufactured and do not undergo further sterilisation during manufacture of the drug product, ensure the DMF includes:

- pre-sterilisation bioburden information for the drug substance and any solvents that may be used after the drug substance has been passed through the sterilising filter for further processing

- details of pre-use and post-use filter integrity testing for sterilising filters used with the drug substance and any solvents
- validation of the bacterial retention properties of the sterilising filters used with the drug substance and any solvents, conducted in the presence of each of the substances/solvents to be filtered
- details of the media fills used to validate the aseptic manufacturing process, including processing times and duration of campaign (if campaign manufacturing is used)
- details of the container/closure system used to contain the sterile drug substance after manufacture. This should include the parameters of the sterilisation processes applied to the container/closure system and confirmation that these have been physically and microbiologically validated to a SAL of 10^{-6}
- validation of container/closure integrity
- results of finished drug substance sterility testing
- results of transport validation.

11.4.3 Products of human or animal origin

The TGA guidance Adventitious agent safety of medicines details the information to be included in the DMF for materials of animal or human origin.

11.4.3.1 Heparin products

Manufacturers that use heparin products should strictly control all the starting materials and intermediates used in the manufacture of the product.

Hence the information that is included in the DMF for heparin should form part of Module 3 of the CTD information provided in support of the drug product.

11.4.3.2 Human albumin

Collection and control of the starting material for human albumin will be described in the plasma master file (PMF). The DMF for human albumin should describe the manufacturing processes used, which is essential to assess the safety of the final product.

Related information and guidance

- Therapeutic goods that contain or are produced from human blood or plasma
- Adventitious agent safety of medicines

11.4.4 Substances produced wholly or in part by fermentation

Guidance on fermentation and nomenclature of substances of natural or semisynthetic origin can be found in the relevant pharmacopoeial monograph of the default standard, such as:

- SC II C, 'Structures and nomenclature of substances of natural or semi-synthetic origin' of the BP.

Related information and guidance

- Note for guidance on quality of biotechnological products: derivation and characterisation of cell substrates used for production of biotechnological/biological products (CPMP/ICH/294/95). This guideline outlines information relating to the manufacture and stability of drug substances produced by fermentation.

In addition to the requirements of the above European Union guideline, further information is required for substances produced wholly or in part by fermentation:

- manufacturing facilities
- manufacturing process and controls
  - pharmaceutical development reports
  - cell growth (propagation) and harvest
  - purification and downstream processing
- control of materials
  - microorganism
  - cell bank system – master cell bank (MCB)
  - cell bank system – working cell bank (WCB)
  - media components
  - solvents, reagents and auxiliary materials
- control of critical steps and intermediates
- noncritical in-process controls
- process validation and/or evaluation
- characterisation
  - structural characterisation
  - physicochemical characterisation
  - biological activity
  - impurities
  - degradation products
- control of intermediates and drug substances
  - specifications
  - analytical procedures
  - validation of analytical procedures
  - reference standards or materials

  - batch analyses
- container/closure system
- labelling
- stability summary and conclusions
  - batch selection for stability studies for fermentation – derived substances
  - expiration date or retest date.

11.4.4.1 Manufacturing facilities

For each facility involved in the manufacture and/or testing of the drug substance (including contract manufacturers and testing laboratories):

- provide the name, address and manufacturing responsibility for the operations or processes performed.

11.4.4.2 Manufacturing process and controls

- Provide a detailed description of the manufacturing process and controls for intermediates and drug substances.
- Describe the entire process, including original inoculum, propagation, harvest, isolation/purification and any modification reactions.

Pharmaceutical development reports

Provide pharmaceutical development reports that describe the scientific rationale for the chosen manufacturing process(es) and controls for fermentation-derived drug substances.

Related information and guidance

- Note for guidance on pharmaceutical development (EMEA/CHMP/167068/2004)

Cell growth (propagation) and harvest

Provide a flow diagram illustrating each step in propagation from the original inoculum (e.g. cells from one or more vials of the WCB) through to the final harvesting operation.

Include relevant information such as:

- the growth conditions
- in-process controls and tests performed (e.g. cell concentrations, volumes, pH, cultivation times, temperatures)

Identify critical steps and intermediates for which specifications are established, along with sampling plans and testing time points.

Include a narrative describing each manufacturing step in the process which identifies and describes:

- all process controls (including critical process controls) and their associated ranges, limits or acceptance criteria

- the intended scale of the process, including the maximum size for a production batch, and seed train expansion, if applicable
- the major equipment involved in each step
- the process for inoculation and each step in propagation, specifying growth conditions
- the media composition at each step of the fermentation process, including water quality, additives used and selection used (i.e. antibiotics, other factors)
- the sterilisation procedures for the equipment (e.g. fermentation vessel), feeds, and other materials used in the fermentation process (dedicated versus general)
- process parameters monitored, and controls for critical steps and intermediates
- procedures used to transfer material between steps
- procedures used to minimise contamination by adventitious agents
- process controls to confirm the effectiveness of the specific manufacturing steps used to inactivate and/or remove adventitious agents
- the criteria for harvesting, including:
  - criteria for rejecting or accepting a fermentation batch if contamination occurs
  - the determination of yields
  - criteria for pooling more than one harvest, if applicable
  - storage conditions and time limits if the harvested crude fermentation product is held before further processing.

Purification and downstream processing

Include a flow diagram and a narrative to describe all the steps involved in isolating the crude fermentation product and purifying it to its final form, along with any relevant information (e.g. volumes, pH, temperatures, holding times).

Identify critical steps and intermediates for which specifications are established, along with testing time points.

Identify all process controls and their associated numeric ranges, limits or acceptance criteria, and include the following:

- methods used in purification or separation of the crude fermentation product (e.g. precipitation, centrifugation, filtration), including major equipment used (e.g. columns, membranes, dedicated/general)
- in-process controls and analytical tests used to characterise the fermentation product (identity, purity and concentration), including levels of process-related and product-related impurities)
- control measures to avoid microbial contamination during purification
- conditions for reuse, and/or procedures for regeneration, of columns, membranes and adsorbents
- storage conditions and time limits if the purified fermentation product is held before further processing.

Describe modification reactions as follows:

Chemical modifications

When a fermentation product is subjected to further molecular change through chemical means:

- include a description of the synthetic steps in the procedural narrative.
- provide a flow diagram of the synthetic process.

Enzymatic modifications

When the fermentation product is further modified using enzymes:

- include the steps in the flow diagram and in the procedural narrative. Additionally, because enzymatic functionality requires carefully controlled conditions (e.g. pH, temperature, osmolarity).
- include detailed information on:
- reaction controls and the optimum range of operation
- the biological source of the enzyme
- how the enzyme is prepared and its purity.
- describe, when appropriate, the operations for reprocessing, reworking, recycling, regeneration and salvaging.

11.4.4.3 Control of materials

Provide a list of materials used in the manufacture of fermentation-derived drug substances, including:

- the microorganism
- cell bank system
- media components
- solvents
- reagents and auxiliary materials
- information on quality and control of materials.

Microorganism

Provide information about the microorganism used for production (genus, species and type strain) and its known genotypic and phenotypic characteristics.

Identify or describe the origin of the source material (or isolate), including methods used to improve the strain.

Cell bank system – master cell bank

Provide a brief description of the procedures used to generate the MCB and the criteria used for qualification, including:

- methods, reagents and media used in preparation
- date of preparation

- process controls
- storage conditions
- procedures used in testing for relevant phenotypic and genotypic markers, and determining culture purity
- procedures used to ensure the absence of contamination with adventitious agents (e.g. microbial contamination and cross-contamination by other cell types), with tests and acceptance criteria specified.

Cell bank system – working cell bank

Preservation of the microbial purity of the MCB is an important factor in maintaining the production strain, and a WCB can be created to lower the likelihood of the MCB being compromised.

A WCB is created by propagating the MCB through defined culture conditions, and then keeping aliquots of the resultant homogeneous culture suspension in individual storage containers of an appropriate size for routine production purposes.

- Provide a brief description of the procedures used to derive a WCB from the MCB and the criteria used for qualification.
- Submit information similar to that submitted for the MCB for the WCB.

Media components

- Provide a list of the media components used at each stage of the fermentation process.
- Provide the specifications for each component that are used to verify that the material is of suitable quality for its intended use.
- Describe the identity and source of any animal-derived materials used in the fermentation media, and how the risk of transmission of transmissible spongiform encephalopathies (TSEs) is controlled.

Solvents, reagents and auxiliary materials

- Provide a list of solvents, reagents, and other auxiliary materials used in the fermentation process.
- Include the specifications for each material that are used to verify that the material is of suitable quality for its intended purpose (including water).

11.4.4.4 Control of critical steps and intermediates

Controls are essential during the fermentation process to ensure consistency of the drug substance.

- Identify and justify all critical process controls and their associated numeric ranges, limits or acceptance criteria.
- Include a brief description of the test. Include experimental data to support the justification.

The manufacturing processes should be controlled to ensure that the drug substance meets previously identified quality attributes.

- Identify all controls used in determining an isolated intermediate's acceptability for downstream processing.

Note

When the intermediate represents the end of the fermentation process and the beginning of a synthetic scheme, the controls warranted are generally more extensive than those used for other types of intermediates.

11.4.4.5 Noncritical in-process controls

Identify and describe noncritical in-process controls.

Note

These controls may not directly demonstrate that a process produces a quality product; however, a description of the tests being conducted and why they are not critical demonstrates understanding of the process.

11.4.4.6 Process validation and/or evaluation

When a fermentation-derived drug substance is sterilised:

- provide the process validation information and data in support of the sterilisation process(es) as per sterile drug substances.

Note

Non sterile process validation is conducted before commercial marketing.

11.4.4.7 Characterisation

Provide confirmation of the structure and characterisation data for fermentation-derived drug substances.

Note

If the fermentation product is a mixture of active components, it may be appropriate to isolate and purify individual components for structural analysis and characterisation.

Structural characterisation

- Provide structural confirmation using physical and chemical techniques (e.g. elemental analysis, mass spectrometry, infrared spectroscopy) for the intermediate or drug substance.
- Include the data and details of its interpretation.

Note

The extent of data needed to confirm the structure can vary, depending on the complexity of the molecule.

Physicochemical characterisation

The type and extent of the physicochemical characterisation information that should be provided depends on:

- the type of drug substance (e.g. semisynthetic molecule, protein)
- the type of dosage form in which the drug substance will be used
- the ability or tendency of the drug substance to occur in one or more solid-state forms
- the importance of differences in the physical characteristics of the different forms to the stability, dissolution or bioavailability of the drug product.

Biological activity

When a biological assay (e.g. antimicrobial activity for antibiotics) is used to assess the potency orstrength of the intermediate or drug substance:

- provide the biological activity data to complete the characterisation profile.
- provide data on the reference standard lot or other relevant lots to demonstrate the potency/strength of the intermediate, drug substance or drug product.

In some cases, the product of fermentation is a complex mixture of major and minor components that together make up a product's biological activity.

When evaluating the impurity profile for these fermentation products, try to identify and characterise the active components (major and minor) that contribute to the product's overall potency and distinguish them from impurities. This may not be practical or feasible in all cases.

Impurities

Provide information about impurities in the fermentation-derived drug substance, such as:

- organic impurities
- inorganic impurities
- residual solvents.

Impurities may be either:

- derived from the manufacturing process (e.g. residual media components, protein and nucleic acids from microbial cells, processing reagents, inorganic salts, filter aids, solvents)
- structurally related to the desired fermentation product but not share the same properties with respect to biological activity, efficacy and safety (e.g. other microbial metabolites, precursors, byproducts).

Process-related impurities derived from fermentation and downstream processing should be minimised through the use of a well-controlled and reproducible manufacturing process.

Structurally related impurities should be identified, tracked and controlled throughout the fermentation, isolation and purification processes.

Provide a summary of the impurities that are most likely to arise during:

- fermentation
- isolation
- purification and storage (e.g. holding time) of the intermediate and the drug substance

Include:

- impurity profiles (i.e. chromatograms)
- test results from representative batches
- results from forced degradation studies used to identify the potential impurities that may arise during storage.

For impurities of known structure, partially characterised or unidentified:

- summarise any studies carried out to characterise the structure of impurities.
- include documentation to show that the analytical procedures used in quantifying impurities are properly validated or qualified.

For specifications for fermentation-derived intermediates, drug substances or medicines include:

- limits for organic impurities
- inorganic impurities
- residual solvents.

Present a rationale for the inclusion or exclusion of impurities in the specifications. As appropriate, this rationale should include a discussion of the impurity profiles observed in batches used for clinical, safety and stability testing, as well as batches representative of the proposed commercial process.

For complex fermentation products

For complex fermentation products that are not well characterised in terms of structure, physicochemical properties, biological activity and purity, the levels for organic impurities should be determined on a case-by-case basis.

The acceptable levels for organic impurities

The acceptable levels for organic impurities will depend on how the fermentation product is to be used.

The levels will likely be less stringent for a drug substance or an intermediate that will be subjected to further modification and/or purification than for a drug product that does not undergo further processing.

For most fermentation products (e.g. antibiotics)

The purification and downstream processing is expected to effectively remove process-related impurities, such as:

- residual media components

- residual protein and nucleic acid derived from microbial cells
- other processing reagents.

Therefore, in most cases, limits do not need to be included in the specifications for these impurities.

However, when studies suggest that process-related impurities are not effectively removed during the purification process, these impurities should be controlled with limits in the specifications, as appropriate.

Note

Microbial impurity tests (e.g. for endotoxins) for medicines may be required.

Degradation products

Summarise details of the degradation products observed during stability studies of the drug substance or drug product, including:

- product-related impurities arising from degradation of the drug substance, and reaction products of the drug substance with an excipient and/or a component of the container/closure system
- test results from representative batches and results from forced degradation studies on the drug substance or product
- studies done to characterise the structure of the degradation products.

Provide documentation to show that analytical procedures used in quantifying degradation products are properly validated or qualified.

Include limits for degradation products that are expected to occur under recommended storage conditions in the specifications for the drug substance or drug product.

Provide a rationale for excluding a degradation product from the specifications.

11.4.4.8 Control of intermediates and drug substances

Specifications

Provide the proposed specifications for the fermentation-derived intermediate, drug substance or drug product, including:

- the tests that will be performed on each batch
- a reference to the analytical procedure used in performing the test
- the acceptance criteria for each test.

Focus the specifications on those characteristics found to be useful in ensuring the safety and efficacy of the intermediate or drug substance.

Provide a justification for the proposed specifications for the intermediate, drug substance and drug product.

For some fermentation-derived drug substances, a nonspecific bioassay (e.g. microbiological assays for antibiotics) may be proposed to determine the content of the drug substance.

In these cases, the development of a specific, stability-indicating assay (e.g. high-performance liquid chromatography [HPLC]) is encouraged because it offers considerable advantages in terms of separation of components, accuracy and precision.

Analytical procedures

Provide copies of the analytical procedures used in testing the fermentation-derived intermediate, drug substance or drug product.

Use specific citations when the analytical procedure is from an official compendium and is not modified in any way.

Validation of analytical procedures

Provide validation data for the analytical procedures used in testing the fermentation-derived intermediate, drug substance or drug product.

Reference standards or materials

Provide information about reference standards or reference materials used for testing.

Relevant information includes:

- characterisation
- storage conditions
- working solutions
- stability of the reference standard.

Batch analyses

Provide batch analysis data, using the proposed analytical procedures and specifications, for:

- all relevant batches of the drug substance (pharmacology and/or toxicology)
- clinical batches for safety and efficacy
- bioavailability/bioequivalence batches
- stability batches
- batches representative of the proposed commercial process.

11.4.4.9 Container/closure system

- Describe the container/closure system for fermentation-derived intermediates, drug substances and drug products, as well as the storage containers for the MCB and WCB.
- Identify the supplier of each component (except for MCB and WCB containers).
- Provide letters of access to master files for raw material component manufacturing.
- Include schematics and raw material specification sheets for the components.
- Include information to support processes for components that are irradiated, pre-sterilised by other means or pre-washed.

11.4.4.10 Labelling

Provide copies of primary and secondary packaging labels for:

- fermentation-derived intermediates (for resale)
- drug substances
- medicines.

Include the following information on the label for intermediates and drug substances:

- name of the chemical entity
- number of units or micrograms of activity per milligram when activity is expressed in biological terms
- number of grams or kilograms in the immediate container
- batch or lot number
- statement 'Sterile' or 'Nonsterile'
- expiration or retest date, as supported by appropriate stability studies
- storage conditions.

11.4.4.11 Stability summary and conclusions

Provide information relating to the stability of the fermentation-derived drug substance.

For intermediates

- the recommendations for stability are applicable to intermediates intended for resale, but generally not otherwise.

Provide a summary of the types of:

- studies conducted
- protocols used
- results from the studies for fermentation-derived intermediates, drug substances and medicines.

For intermediates and drug substances

Provide conclusions regarding appropriate storage conditions and an appropriate retest or expiration date.

Batch selection for stability studies for fermentation–derived substances

Studies should be conducted on three separate batches (if feasible, generated from three different WCB vials).

The batches can be pilot scale; however, the manufacturing process for the pilot-scale batches should fully represent and simulate the proposed full-scale production process.

Expiration date or retest date

For fermentation-derived drug substances

A retest period or date may be appropriate in cases where the drug substance shows little change in potency and/or degradation products throughout the proposed shelf life.

Use an expiration date if there is a marked change or trend in the potency and/or degradation profile, such that there is a concern that an out-of-specification test result could occur during stability studies.

Expiration date

When an expiration date is assigned to a fermentation-derived intermediate or drug substance, the material is not to be used beyond that date and is to be discarded if that date has passed.

Retest date

A retest date is a date before which the material meets all applicable specifications.

Beyond that date, the material may be retested and, if acceptable, used within a reasonable amount of time (e.g. within 30 days).

The retest date should include the test attributes that are critical to the fermentation-derived intermediate or drug substance (e.g. potency, moisture content).

Expiration dates and retest dates should both be established based on supportive stability data.

For fermentation-derived medicines

- An expiration date should be established based on supportive stability data.
- Retest dates are not appropriate for fermentation-derived medicines.

11.5 When to include a certificate of suitability in an application

A CEP may be submitted instead of a DMF:

- for a Category 1 application to register a new prescription medicine.
- for a request to make a variation to include an additional site of drug substance manufacture.
- when a drug substance manufacturer ceases the operation of a DMF and refers to a CEP instead.

For ingredients of animal or human origin

A CEP does not contain sufficient information and will not alone be accepted.

Related information and guidance

- Therapeutic goods that contain or are produced from human blood or plasma
- Adventitious agent safety of medicines

11.6 How to include a certificate of suitability in an application

Sponsors need the written permission of the drug substance manufacturer to refer to a CEP in an application.

A proforma for a *Letter of Access* (available in Module 1.6.3 of the CTD) from the drug substance manufacturer, addressed to the TGA and indicating clearly the product sponsor to which it applies, should be sent directly to the TGA, either with the CEP or separately.

Note

The proforma for *Letters of Access* used in Europe is not acceptable.

11.7 Sponsor's obligations regarding certificates of suitability

Sponsors:

- have an obligation under the standard conditions of registration, imposed under s. 28(3) of the Act, to ensure that no changes are made to the product, including the drug substance, without the sponsor's knowledge and TGA approval (if required).
- need a formal agreement with the manufacturer of the drug substance to ensure they are notified before any changes are made to the drug substance.
- are required to seek approval for any changes made to the drug substance after the CEP has been issued.

Note

Amendments to the CEP that are allowed by the EDQM are not automatically accepted in Australia. An amended CEP can be submitted in support of a request to make a variation to an Australian Register of Therapeutic Goods (ARTG) entry.

Related information and guidance

- Minor variations to registered prescription medicines: Chemical entities

11.8 Additional information regarding certificates of suitability for some drug substances

Further information is required by the TGA for the following types of drug substances.

11.8.1 Nonsterile drug substances

Sponsors provide:

- written authorisation from the drug substance manufacturer in the form of a *Letter of Access* (available in Module 1.6.3 of the CTD) for the TGA to refer to the CEP.
- written assurance that no significant changes have been made to the manufacturing method since the CEP (or its last revision) was issued by the EDQM, including to the scale of the final purification step.
- written assurance that the drug substance complies with all conditions and additional tests attached to the CEP by the EDQM.
- written assurance that for currently registered drug products, any tests and limits required by the TGA in addition to those in the Ph. Eur. monograph (e.g. particle size distribution, specific polymorphic form) that are relevant to the intended use of the substance will be applied to each batch of the drug substance that is destined for the Australian market.
- certificates of analysis (or equivalent analytical data) for at least three production-scale batches demonstrating that the drug substance complies with the monograph, any additional tests or limits attached to the CEP and, for currently registered drug products, any agreed additional tests or limits for the drug substance.
- the chemical structures of the impurities if the CEP refers to impurities as a code number.
- a list of the changes between the previously approved version of the DMF or CEP and the current version of the CEP for an updated CEP or for a change from a DMF to a CEP.

Note

If this information is confidential from the sponsor, the TGA may obtain this information from the CEP holder.

11.8.2 Sterile drug substances

In addition to the nonsterile drug substances requirements listed above, a CEP is not sufficient for the TGA to assess the quality of a sterile drug substance (and/or excipients) that does not undergo further processing. Information regarding sterile manufacture, as specified in What to include in a Drug Master File for sterile drug substances, must be provided, but a full DMF is not required.

11.9 Other information that may be requested by the TGA in relation to certificates of suitability

The TGA may request:

- additional information about the manufacture and quality control of the drug substance
- additional information about how the impurity limits specified in the CEP have been justified by the manufacturer and assessed by the EDQM
- copies of the EDQM evaluation report parts A and B and any related correspondence between the manufacturer and the EDQM
- validation data for use of the drug substance in the drug product, where relevant.

Therapeutic Goods Administration

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Reference/Publication #