Australian Government
Department of Health
Therapeutic Goods Administration

Mandatory requirements for an effective application

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TGA Health Safety Regulation

Contents

Overview

This guidance describes the information that must be submitted to the TGA for prescription medicine applications to be considered effective and proceed to evaluation. To the extent that the Pre-submission Planning Form (PPF) is a reflection of the dossier to be submitted, these requirements apply equally to Milestone 1 and Milestone 2 of the registration process.

Appendix A - Specific mandatory requirements describes the common application issues and deficiencies we have identified.

Section 23B of the *Therapeutic Goods Act 1989* (the Act) states the requirements relating to prescription medicines applications.

In this document (*'Mandatory requirements for an effective application'*), the following terminology is used:

- an effective application means an application that has been determined to pass preliminary assessment
- a not effective application means an application that has been determined to not pass preliminary assessment.

Scope

These requirements apply to applications lodged with the TGA:

- to register a new prescription medicine (excluding applications to register an Additional Trade Name and applications to which Regulation 16G applies)
- to vary the register entry for a prescription medicine that involves clinical, nonclinical, or bioequivalence data.

Legislative requirements

Applications for new registrations

Applications for new registrations[1] are made under Section 23 of the *Therapeutic Goods Act 1989* (the Act). Section 23B(2) requires that applications:

- are made using a form approved by the Secretary;
- include information in a form approved by the Secretary; and
- include such information as will allow the determination (preliminary assessment) of the application.

[1] A new registration is one that requires a new ARTG entry by reason of being separate and distinct goods under section 16 of the Therapeutic Goods Act 1989. This includes new chemical entities, new strengths, new dosage forms, different directions for use, formulation changes, changes in trade name, extension of indication etc. By the provisions in the Therapeutic Goods (Groups) Order 2001, not all new registrations will result in a new AUST R number being allocated if they are taken to be grouped.

Applications referred to in regulation 16C of the Regulations (including, Category 1 and Comparable Overseas Regulator (COR) report-based applications for new registrations, other than applications for an additional trade name) must comply with the following regulatory documents:

- Pre-submission planning form (PPF)
- One of:
  - prescription medicines electronic lodgement facility (TGA Business Services), or
  - Application for the registration, or to vary the conditions of registration, of prescription medicines.
- Mandatory requirements for an effective application (this guidance)
- CTD Module 1: Administrative information and prescribing information for Australia
- Module 2: being overviews, written summaries and tabulated summaries of the data contained in the Modules 3, 4 and 5 as described below
- Module 3: ICH M4Q Common technical document for the registration of pharmaceuticals for human use - Quality (CPMP/ICH/2887/99 Rev 1 Quality)
- Module 4: ICH M4S Common technical document for the registration of pharmaceuticals for human use - Safety (CPMP/ICH/2997/99 Rev 1 Safety)
- Module 5: ICH M4E Common technical document for the registration of pharmaceuticals for human use - Efficacy (CPMP/ICH/2887/99 Rev 1 Efficacy)

The following guidance will assist applicants in the preparation of a PPF and an application dossier:

- Prescription medicine registration process
- COR report-based process guidance
- Priority review registration process
- Information for applicants completing a pre-submission planning form
- Electronic submissions
- General dossier requirements

Any departures from relevant requirements or guidelines must be explicitly justified in the application dossier. Some departures may require prior liaison with the TGA. See Justifications below for further information.

In submitting a PPF, the applicant is indicating they understand and agree to comply with the General dossier requirements for a dossier to be considered effective and accepted for evaluation.

Applications for variations

Applications requesting a variation to an existing registration are made under section 9D of the Act.

Legislative instruments issued under section 9D(6)(a) and section 9D(6)(b) describe the form and manner approved by the Secretary for applications made under section 9D(3), including the requirement to provide a dossier in CTD format.

For section 9D(3) applications to which regulation 16D of the Therapeutic Goods Regulations 1990 applies (i.e. Category 1 and COR report-based applications for variations), the legislative instruments set out a set of requirements similar to those for new registrations (above). The supporting documents listed above as applicable to new registration applications also apply to applications for variations.

Note

As with applications for new registrations:

- Any departures from relevant requirements or guidelines must be explicitly justified in the application dossier. Some departures may require prior liaison with the TGA. See Justifications below for further information.
- In submitting a PPF, the applicant is indicating they understand and agree to comply with the TGA's requirements for a dossier to be considered effective and accepted for evaluation.

Content of application dossier

The exact content of the application dossier will vary according to the:

- application category
- nature of the medicine
- application type.

A dossier documents matrix is provided in CTD Module 1: Administrative information and prescribing information for Australia which provides a high-level overview of the application dossier CTD section requirements for different application types.

Overview of CTD documents

CTD Module 1: Administrative information and prescribing information for Australia establishes the Module 1 content for different application types.

CTD Module 2 is a summary module which provides an overview of the information/data provided in the quality (Module 3), nonclinical (Module 4), and clinical (Module 5) modules of the dossier. Information on the content of Module 2 is provided at the beginning of CTD Modules 3, 4, and 5.

The organisation of Modules 3, 4, and 5 is specified by the CTD Modules 3, 4, and 5. These modules contain headings and sub-sections under which applicants must insert technical data. To determine technical data requirements, applicants must consult relevant Australia-specific guidelines and EU guidelines adopted in Australia.

Technical data requirements

The application dossier must provide appropriate documentation (in the correct format and locations, as determined by the CTD modules), including outcomes of trials and studies, to allow

the Delegate of the Secretary to assess quality, safety, and efficacy claims. The technical data requirements that establish the documentation to be provided in the dossier are:

- Australia-specific requirements are identified in CTD Module 1: Administrative information and prescribing information for Australia and TGA guidelines.
- EU guidelines adopted in Australia - guidelines prepared by the European Committee for Medicinal Products for Human Use (CHMP) and/or those prepared within the ICH process that have been adopted by the TGA.

The use of EU guidelines adopted in Australia and other Australia-specific guidelines is not mandated in the legislation. However, section 25(1) of the Act requires that when making a decision on whether to approve a medicine for registration, the delegate determines:

> *"whether the quality, safety and efficacy of the goods for the purposes for which they [the goods] are to be used have been satisfactorily established;"*

Where a dossier does not address the applicable requirements/guidelines, or fails to adequately justify why an applicable requirement/guideline has not been addressed in the application, we may be unable to establish satisfactorily the quality, safety or efficacy of the proposed good.

Justifications

As noted above, Australia-specific guidelines and adopted EU guidelines determine the data and information required in Modules 1, 2, 3, 4, and 5 of a dossier to demonstrate quality, safety, and efficacy.

It is the applicant's responsibility to familiarise themselves with all relevant Australia-specific guidelines and EU guidelines adopted in Australia, and to advise us of instances of, and reasons for, deviation from the applicable guidelines or requirements.

A justification is a reason given by the applicant for not complying, in the application dossier, with a specific requirement or guideline, and generally fall into one of two broad categories:

- Justifications that will determine the **categories/sections of information** required in the application dossier for it to be considered effective and accepted for evaluation. If a dossier does not contain a certain section, and an acceptable justification has not been provided for its absence, the application dossier may not meet the requirements for an effective application under section 23B of the Act.
- Justifications that will determine the **depth and breadth, or adherence to an adopted standard specification or guideline** for the required information. This is relevant to evaluation during the 1st and 2nd round assessment phases when the content of the application dossier is being evaluated.

If the justification provided by the applicant for not adhering to a specification or guideline is not present, not appropriate (e.g. wrong guideline is addressed), or inadequate, the application submitted may not satisfactorily establish the quality, safety and efficacy of the proposed good. That is, the application will not be considered to be effective.

Some justifications must be submitted to us prior to lodging a Pre-submission planning form (PPF) and our acceptance of the justification included with the PPF. These include:

- justification of a new fixed dose combination
- justification of the literature search strategy for a literature-based submission.

The PPF refers to several justifications required to be submitted with the form:

- for a generic application, a justification where a salt/ester of the generic product is different to the Australian reference product
- for applications where the existing ingredients intended are to be used for different purposes (e.g. new route of administration), a justification is required if not providing additional toxicology data to support the safety of the ingredient for the intended use
- justifications for not providing data according to a particular guideline or aspect of a guideline
- justification for including a preservative in a single dose injection.

Where the applicant chooses not to provide data according to a particular guideline or aspect of a guideline (for example, the applicant may consider the guideline is not applicable to the product), the justification must explain why the guideline is not applicable and why the proposed alternative is valid.

A justification must be scientifically robust and address the relevant requirement. For certain requirements, we provide detailed information to assist applicants in constructing a robust scientific justification (for example, the TGA Biopharmaceutic studies guideline provides information on the required content for a justification for not conducting biopharmaceutic studies).

Where we have provided such detailed information, the applicant must ensure all details have been addressed in the justification. In other cases, applicants must adhere to the principles of a robust scientific justification (see Important note below).

Important note

Where possible applicants should not deviate from the relevant guidelines.

Should an applicant submit an application that includes justifications for not meeting a relevant guideline, we will assess whether the justification provided is a robust scientific justification.

A robust scientific justification is one that:

- clearly identifies the guideline or part of the guideline that is not being met
- specifically addresses why the guideline is not being met
- has a contemporary scientific basis
- includes citations to the relevant reference documents, including TGA documents, where appropriate. Applicants must ensure all such references are included in the dossier.

This justification will be assessed in the above terms - but not evaluated - in determining whether an application is to be found effective.

Administrative requirements

Applicants must comply with (and cannot provide a justification for not complying with) the administrative requirements. These include those applying to:

- forms to be completed for administrative purposes
- the presentation of the electronic dossiers

- requirements specific to the Priority review registration pathway

Establishing bioequivalence or therapeutic equivalence

Biopharmaceutic studies of new medicines typically include the investigation of absolute bioavailability, relative bioavailability and bioequivalence of different dosage forms or formulations, and the effect of food or antacids on their bioavailability.

For new generic medicines, establishing bioequivalence with the Australian reference product allows bridging to the nonclinical and clinical studies. Applicants applying for a new generic medicine are therefore required to provide information to demonstrate bioequivalence; however, our experience is that many applicants are uncertain about how to do so.

There are several Australian and adopted EU guidelines that are relevant to establishing bioequivalence. A summary of these documents, and their relationships, is provided below.

Document	Relevant to	Comments
TGA guideline: Biopharmaceutic studies	All applications to register a new medicine.	Applicants should consult this guideline to ascertain: • whether or not biopharmaceutic studies will be required to support their application in Australia. • minimal issues to be addressed if providing a justification for not submitting biopharmaceutic data. • issues to consider concerning the choice of reference product. If it is unclear whether a medicine is of the category *Prescription medicines which do not require biopharmaceutic data*, the applicant should contact us prior to lodging the PPF.

Document	Relevant to	Comments
Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr)	Applications for synthetic medicines with an immediate release formulation and systemic action.	While this guidance suggests that the design and conduct of the study should follow EU regulations on Good Clinical Practice, applicants should note that the EU *Note for Guidance on Good Clinical Practice* (CPMP/ICH/135/95) has been adopted in Australia with TGA annotations. The procedure for abridged applications claiming essential similarity to a reference product (i.e. generics), which allows applications to be made to numerous Member States of the EU, based on bioequivalence with a reference product from one Member State, does not apply in Australia. A bioequivalence study to support the registration of a generic product in Australia should use a reference product obtained in Australia. Where an overseas reference product is used, the applicant must be able to demonstrate the overseas and Australian reference products are identical (see TGA guideline Biopharmaceutic studies).

Document	Relevant to	Comments
Clinical Requirements for Locally Applied, Locally Acting Products, Containing Known Constituents (CPMP/EWP/239/95)	Applications for synthetic medicines that are applied locally and act at the site of application.	Locally applied products that do not act at the immediate site of application (skin, cornea etc.) are not covered by this guideline. For example, eye drops that exert their effect beyond the cornea (i.e. the deeper tissues of the eye). Examples of such eye drops include eye drops for the treatment of glaucoma. Requirements for establishing the bioequivalence of such products to a reference product are set out in the adopted EU Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1). Products applied in a transdermal dosage form are not covered by this guideline – refer to the Note for Guidance on Modified Release Oral and Transdermal Dosage Forms. Section II (Pharmacokinetic and Clinical Evaluation) (CPMP/EWP/280/96)

Document	Relevant to	Comments
Note for Guidance on Modified Release Oral and Transdermal Dosage Forms: Section II (Pharmacokinetic and Clinical Evaluation) (CPMP/EWP/280/96)	Applications for synthetic medicines in transdermal and modified release oral dosage forms.	For multiple strengths of generic transdermal and modified release oral dosage forms, bioequivalence studies should be performed at least on the lowest and highest strengths versus the corresponding reference products. If an applicant considers that this is unnecessary in a particular case, a justification for not submitting bioequivalence data should be submitted in accordance with the TGA guideline Biopharmaceutic studies (Justification for not submitting biopharmaceutic data).
Guideline on Similar Biological Medicinal Products (CHMP/437/04) and related guidelines	Applications for new biological medicines that are similar to an existing reference product	Applications for similar biological medicinal products are not considered new generic applications. Applicants should follow the approaches developed in the adopted EU guidelines.

Document	Relevant to	Comments
Various clinical guidelines for medicines for specific therapeutic products or use	Applications requiring non-inferiority studies	Some clinical guidelines provide additional information about the studies needed to demonstrate therapeutic equivalence for specific therapeutic products or use. However, applicants must ensure the guidelines are relevant to their particular application/product. For example, the guideline: Clinical Investigation of corticosteroids intended for use on the skin refers to the use of a vasoconstriction assay. This is an example of a pharmacodynamic endpoint that is not related to the therapeutic effect of the medicinal product. When using a pharmacodynamic model to replace clinical data, applicants must ensure the model chosen is internally valid. In the case of the vasoconstriction assay this endpoint may not be externally valid where the composition of the generic product differs to that of the reference product. The use of pharmacodynamic endpoints should be justified in terms of their direct relevance to the intended therapeutic effect of the active component of the medicinal product.

Applicants should note that the TGA considers newly released and updated EU guidelines and decides whether or not to adopt them. Some of the above guidelines may therefore be amended, removed or replaced from time to time. Applicants should check the TGA website routinely and subscribe to receive email updates on new content.

Appendix A - Specific mandatory requirements

General

Section	Issue	Requirement
All	Language	See General dossier requirements – Part A
All	Measurements	See General dossier requirements – Part A
All	Provision of Module 1	All application dossiers must include Module 1. The required content of the Module 1 is described in *CTD Module 1: Administrative information and prescribing information for Australia*.
All	Electronic Data	See General dossier requirements – Part B Applications must be submitted in eCTD format to be eligible for Priority review or the COR report-based process.
All	Applications that have previously been rejected by the TGA or withdrawn by the applicant before a decision by the TGA Delegate.	Applicants must identify in the letter of application how the deficiencies identified in the previous application have been addressed. To ensure that the data to be evaluated by the TGA are the current data relevant to that application, the applicant must provide: A complete, up-to-date electronic data set for each new application. A complete new Module 1 plus replacement for those volumes that have changed, plus any additional volumes. The letter of application must specify which modules and data volumes from the previous application should be used for the current application. Data previously submitted to us must be clearly identified in the Table of Contents of the dossier.

Module 1: Administrative information and prescribing information for Australia

Section	Issue	Requirement
All	Requirements in *CTD Module 1 – Administrative information and prescribing information for Australia*	The application must meet all the relevant administrative and Module 1 requirements described in *CTD Module 1: Administrative information and prescribing information for Australia*.
1.0	Letter of authorisation	• If an applicant is acting on behalf of another applicant, a letter of authorisation must be provided. • Where the applicant is using another company's name and/or livery on labels, a letter of authorisation from the company owning the name/livery must be provided.
1.2.1	Evidence of Good Manufacturing Practice (GMP)	• The application must meet GMP requirements outlined in Manufacturing principles for medicinal products • Under the COR report-based process: – COR-A applications must include evidence of compliance with GMP (a current GMP licence or clearance number for all relevant manufacturing sites) – COR-B applications must include evidence that the applicant has applied for a GMP clearance, licence or certification and paid the associated fee(s) for each manufacturing site. • To be eligible for Priority review, applicants must: – provide evidence of compliance with GMP (a current GMP licence or clearance number for all relevant manufacturing sites); or – demonstrate they have applied for a GMP clearance, licence or certification and paid the associated fees for each manufacturing site.

Section	Issue	Requirement
1.5.1	Determination/Designation	• To be eligible for Priority review, applicants must provide a copy of the Priority review determination letter that was issued by the TGA. The determination must be in force at the time of making the application. • To be eligible for a waiver of the section 23 application fees (for Priority or standard pathways), applicants must provide a copy of the Orphan drug designation letter that was issued by the TGA. The designation must be in force at the time of making the application.
1.8	Information relating to pharmacovigilance	The risk management plan (if required) is to comply with requirements as set out in TGA guidance: Risk management plans for medicines and biologicals. The Risk Management Plan should be the current, unaltered EU-RMP (if available) and an Australian Specific Annex should be included. An alternative to the EU RMP is acceptable **only** if there is no current EU-RMP (see Risk management plans). All attachments, annexes and appendices referred to in the RMP should be in English and included in full in electronic form.
1.8.3	Declaration of compliance with PPF and planning letter	• In Module 1.8.3, applicants must provide a declaration of compliance with the information provided about the application(s) in the PPF (including attachments) and planning letter. • The declaration must also address any issues that we raised in the planning letter, and identify how the issues were resolved in the application.
1.11.2	Justification for not providing appropriate biopharmaceutic studies (overseas reference product)	A justification for not providing biopharmaceutic studies against an Australian sourced reference product must be provided where the biopharmaceutic data provided have been generated against an overseas reference product. **Note:** See Module 5 section in this document for further information and requirements about when this document must be provided.

Section	Issue	Requirement
1.11.2	Justification for not providing appropriate biopharmaceutic studies (studies not provided for some or all products)	A justification for not providing appropriate biopharmaceutic studies must be provided where biopharmaceutic data are required (TGA guideline Biopharmaceutic studies - Medicines that require biopharmaceutic data) but have not been provided for one or more products. Such a justification must consist of a document that: • provides an accurate, robust and scientific response to each point/heading listed in Biopharmaceutic studies - Justification for not submitting biopharmaceutic data • provides any other information relevant to the justification in separate section/s, and • addresses any other aspects from relevant EU guidelines adopted in Australia (for example, *Guideline on the investigation of bioequivalence* CPMP/QWP/EWP/1401/98 Rev 1). **Note:** See Module 5 section in this document for further information and requirements about when this document must be provided.

Module 2 - CTD Summaries

Section	Issue	Requirement
2.4	Generic applications	A Module 2.4 must be supplied for all new generic applications where the active ingredient is a different salt/ester from the Australian reference product's active ingredient. A Module 2.4 must also be supplied where the levels of impurities and degradants lie outside the levels permitted in ICH guidelines. Except for biotechnology-derived products, an assessment of the impurities and degradants present in the drug substance and product should be included along with what is known of their potential pharmacologic and toxicologic effects. This assessment should form part of the justification for proposed impurity limits in the drug substance and product, and be appropriately cross-referenced to the quality documentation.

Section	Issue	Requirement
2.5	Generic applications	Module 2.5 must be supplied for all new generic applications.
2.7	Generic applications	Module 2.7 must be supplied for new generic applications where biopharmaceutic studies have been provided in support of the application.

Module 3 - Quality

Section	Issue	Requirement
3.2.S	Drug substance (name, manufacturer)	There are four options for providing the supporting data for the drug substances (active ingredients) in a product. One of these options MUST be used: • drug master file (DMF) submitted • certificate of suitability (CEP) submitted • confirmation that all aspects of drug substance manufacture (including sterile manufacture, if applicable) and control has been previously approved by the TGA • drug substance is fully described in Module 3.2.S. **Note:** If the drug substance is sterile and is not subjected to further sterilisation during finished product manufacture, a CEP alone does not provide sufficient information for evaluation of sterility aspects. It may be submitted in conjunction with one of the other options (TGA Drug master file guideline).
3.2.S	If a DMF is submitted	• The full quality control specifications applied to the drug substance by the drug product manufacturer must be provided in Module 3.2.S. • If the drug substance is sterile and not subjected to further sterilisation, then full details of sterile manufacture, its validation and associated microbiological validation of container integrity and transportation, if applicable, must be provided as per guidance in 3.2.P and 3.2.P.7. • Batch analytical data generated by both the drug substance and the drug product manufacturer(s) must be supplied for typical batches of drug substance from each supplier. • If a DMF for a biotechnological drug substance is submitted, it should contain the data required under 'If the drug substance is fully described in Module 3.2.S.
3.2.S	If a CEP is submitted	• Documentation detailed in the TGA Drug master file guideline and Module 1.6 of the CTD must be provided.

Section	Issue	Requirement
3.2.S	If all aspects of a drug substance manufacture (including sterile manufacture, if applicable) and control has been previously approved by the TGA	• Details and scientific justifications must be provided of any additional tests and requirements (e.g. for particle size distribution, polymorphic form) applied to the bulk drug substance before use in the manufacture of the drug product(s) covered by the current application. • Detailed validation data must be provided for these additional tests. • Representative batch analytical data must be provided.

Section	Issue	Requirement
3.2.S	If the drug substance is fully described in Module 3.2.S	• For biotechnology products: – a flow diagram of the synthetic process(es) must be provided. – protein and DNA sequences of the drug substance must be provided. – characterisation data, including post-translational modifications and functional characteristics of product-related substances as detailed in *The EU guideline 3AB1a "*Production and Quality Control of Medicinal Products derived by recombinant DNA Technology*" Section 7,* must be included*.* – a complete description of the manufacturing process including fermentation, modification reactions and purification should also be included. – full data describing development genetics, generation of cell substrate, cell banking and cell bank stability, including diagrams and sequence(s) of the vector(s), must be provided (see ICH Topic Q5E: Comparability of biotechnological/biological products). – full batch release specifications and validation of test methods used must be provided. – detailed validation data for all critical steps. • For similar biological medicinal products, additional characterisation studies consistent with ICH Topic Q 5 E: "Comparability of Biotechnological/ Biological Products Note for Guidance on Biotechnological/Biological Products Subject to Changes in their Manufacturing Process" must be provided to demonstrate comparability with reference product. • If the drug substance is sterile and not subjected to further sterilisation, then full details of sterile manufacture, its validation and associated microbiological validation of container integrity and transportation, if applicable, must be provided as per guidance in 3.2.P and 3.2.P.7.
3.2.S	If any raw material or excipient is plasma derived	• The epidemiological data for the previous calendar year must be provided.

Section	Issue	Requirement
3.2.S.4.3	Validation of test methods	• Detailed validation reports for each test method must be provided. If a PMF is submitted, these reports should be within the PMF. • All raw data supplied (e.g. SDS-PAGE photos or HPLC traces) must be clear and legible.
3.2.P	Drug product (name, dosage form)	• The composition of each product and strength must be clearly defined. • All proprietary and non-proprietary ingredients must be listed as Australian Approved Names (AANs), Australian Biological Names (ABNs) Australian Herbal Names (AHN), or appropriate documentation submitted to the TGA for a new AAN/ABN/AHN to be created (also see 1.2.2 and Module 4). • Safety data (nonclinical and/or clinical) must be provided for: – any new ingredient which has not been included in the ARTG previously – any ingredient administered via a new route of administration or intended to be used for a different purpose. • If tablets are scored, data must be provided to confirm that splitting is clean and the portions produced comply with pharmacopoeial limits for uniformity of weight/content. • For modified release dosage forms, investigation of the effect of ethanol on *in vitro* dissolution/release must be included. • Detailed validation data must be provided for all critical steps in the manufacturing process (including any cleaning and/or sterilisation steps). For sterile drug products, validation data must be included and must cover the following: • For all drug products, bioburden information including presterilisation bioburden limits and for extended processing times (including hold times), evidence to show that sterility or microbiological quality (as applicable) is not compromised. **Note:** we expect that bioburden information including a specification for pre-sterilisation bioburden limits will be provided for all applications for market authorisation, not just for those with certain sterilisation procedures. • Drug products that are sterilised by filtration and

Section	Issue	Requirement
		aseptically filled or aseptically manufactured (as applicable): – Containers/closures: § parameters of the sterilisation processes and confirmation that these have been physically and microbiologically validated to a sterility assurance level (SAL) of 10^{-6} § statement that processes to remove endotoxin have been validated to demonstrate a reduction in endotoxin units of > 3-log. – Sterilising filter: § confirmation that the membrane filter is tested for integrity before and after use § validation of the bacterial retention capabilities of the filter conducted in the presence of the product. – Statements of maximum permitted processing (holding, storage and filling times) during manufacture. – Media fill studies to validate the aseptic manufacturing process. Media fill studies should be conducted under worst case conditions including maximum processing and filling times, and should include simulation of all aseptic manufacturing processes, including those using previously sterilised components. – For terminally sterilised drug products or sterilised drug substances or excipients not subjected to further sterilisation: § physical and microbiological performance qualification studies and confirmation that these studies show that a SAL of 10^{-6} is achieved throughout the maximum and minimum loads. • Statements of processing times (e.g. from start of compounding until terminal sterilisation).

Section	Issue	Requirement
3.2.P.5	Control of drug product	• The proposed specifications for the finished product must be provided. • Impurity limits that are above the ICH threshold(s) must be qualified by toxicology data or by reference to an appropriate pharmacopoeial monograph. For generic medicine applications, limits above the ICH threshold may also be qualified by comparison with the Australian reference product near or just past expiry date. • For endotoxin testing, the applicant must provide the bacterial endotoxin specification, based on either the monograph limit or on the maximum human dose per kg. • For sterility testing, the applicant must provide a statement that sterility testing is performed according to the current version of the harmonised pharmacopoeial (USP/BP/ Ph Eur) method.
3.2.P.5.2	Analytical procedures	Detailed description of all in-house test methods must be provided.
3.2.P.5.3	Validation of test methods	Detailed validation reports for each test method must be provided, except for pharmacopoeial test methods. For Bacterial Endotoxin testing, this validation should follow Ph. Eur. 5.1.10. *Guidelines for using the test for Bacterial Endotoxins*, particularly noting 13-2 requiring the test for interfering factors to be performed on 3 production batches. All raw data supplied (e.g. SDS-PAGE photos or HPLC traces) must be clear and legible.

Section	Issue	Requirement
3.2.P.7	Container closure system	The immediate and outer packaging and packaging materials (e.g. type of glass or plastic), pack sizes, any dosing device, any induction seals and any desiccant or cotton wool contained in the package must be defined and described – samples are not required. Details of the stopper formulation and appropriate leaching studies provided. The full specifications and routine tests on the proposed marketing containers and closures must be provided. If the drug product is packaged in a child-resistant container, an assurance must be provided of the tests that have been performed to ensure that the child-resistant properties of the packaging are not affected by the contents and are retained throughout the product shelf-life, including during routine use. An assurance must be provided that full details of compliance are held by the applicant and are available for submission to the TGA upon request. For sterile injectable drug products, the following must be provided: • for containers closed by fusion (i.e. ampoules), confirmation that containers are subjected to 100% integrity testing • for containers closed by other means (i.e. vials, syringes), information on container/closure integrity tests such as dye penetration or microbial ingress tests • for multi-dose injectables, confirmation that additional integrity tests are as per Ph Eur 3.2.9.

Section	Issue	Requirement
3.2.P.8	Stability	In the case of liquid drug products in a stoppered container, stability trials carried out on the product stored in the inverted position must be provided. If there were any changes in test procedures during the course of the trials, comparison and correlation of results generated by the alternative methods must be provided. For multi-dose products, the following must be provided: • information on antimicrobial preservative efficacy data at the beginning and end of the closed shelf life, as specified in TGO 77 Microbiological Standards for Medicines • information on microbiological challenge testing/simulated use testing as applicable, to support the open shelf life (in-use) period. In the case of biological products, no less than 6 months real-time stability data should be supplied and the shelf-life allowed will be no more than the amount of real-time data supplied. In the case of chemical entities, no less than 6 months real-time and accelerated stability data must be provided. For non-conventional, including modified release, dosage forms, no less than 12 months real-time and 6 month accelerated stability data must be provided.

Section	Issue	Requirement
3.2.A.2	Adventitious Agent Safety	**Non-viral adventitious agents** (e.g. transmissible spongiform encephalopathy agents and mycoplasma): - detailed information should be provided on the avoidance and control of these agents - this information could include, for example, certification and/or testing of raw materials and excipients, and control of the production process as appropriate for the specific material. The applicant should refer to European Pharmocopeia (Ph.Eur.) – 5.2.8, EMA/410/01 and TGA Guidance 10: Adventitious agent safety of medicine for further guidance. **Viral Adventitious Agents**: Detailed information for the following aspects of viral safety of the product should be provided in relation to all stages of product development and production: - Materials of biological origin – related to information in Sections 3.2.S.2.3 and 3.2.P.4.5. Cell line qualification should be included in this assessment. - Testing at appropriate stages of production and viral testing of unprocessed bulk – details and results of testing during manufacturing to demonstrate that the product is free from viral contamination at appropriate stages of manufacture. Related to information provided in Sections 3.2.S.2.4 and 3.2.P.3.4. - Viral clearance studies – rationale and action plan for assessing viral clearance, and results and evaluation of viral clearance studies. Related to Sections 3.2.S.2.5 and 3.2.P.3.5. The applicant should refer to ICH Guidelines Q5A, Q5D, Q6B and TGA Guidance 10: Adventitious agent safety of medicine for further Guidance.

Module 4 - Safety (nonclinical study reports)

Section	Issue	Requirement
4	Nonclinical data for category 1 application type: • new chemical entity (new salt ester) • new chemical entity (new combination of active ingredients) • major variation (new route of administration; change in dosage, dose regimen or maximum daily dose; change in patient group) • generic application (new isomer, mixture of isomers, complex of, derivative of or salt of a registered substance)	Nonclinical data or a scientific justification for the absence of nonclinical data must be provided.
4	Excipients	If the medicine contains an excipient used for the first time in a therapeutic product in Australia, an assessment of the information relating to safety must be provided in the nonclinical overview (Module 2.4). Nonclinical data must be provided for a new excipient, an excipient with a new route of administration or an increased daily dose or a justification for not providing data must be included in the application. Also see 3.2.P.
4	Impurity qualification	Toxicology data (Module 4) or a scientific justification (Module 2.4 and/or Module 4) for impurities that are above the ICH qualification threshold must be provided. An assessment of this information must be provided in the nonclinical overview (Module 2.4).

Module 5 - Efficacy (clinical study reports)

Section	Issue	Requirement
5.3.1	Generic medicine: Establishing clinical equivalence	For all new generic applications, applicants must provide appropriate information to demonstrate clinical equivalence of the proposed product with the corresponding Australian reference product, unless specifically precluded by listed in Biopharmaceutic studies – Medicines which do not require biopharmaceutic data. Clinical equivalence is to be demonstrated through: • bioequivalence studies • a Biopharmaceutics Classification System (BCS)-based biowaiver approach (see *Guideline on the investigation of bioequivalence*, CPMP/EWP/QWP/1401/98 Rev. 1/Corr), • a robust scientific justification prepared in accordance with Biopharmaceutic studies - Justification for not submitting biopharmaceutic data (and any other relevant guidelines) and included in Module 1.11.2 • or a combination of the above. If bioequivalence studies are not appropriate (for example, topical products) then pharmacodynamic and/or clinical non-inferiority studies may be necessary. **Note:** Additional specific requirements in relation to biopharmaceutic studies for a number of common scenarios are set out below.
5.3.1	Generic medicine: Immediate release oral dosage forms	Comparative bioavailability data must be provided to establish the bioequivalence of the generic medicine and the corresponding reference product in Australia, unless the applicant either: • Provides a robust, scientific justification prepared in accordance with Biopharmaceutic studies – Choice of the reference product for bioequivalence of generic medicines at Module 1.11.2; or • Adopts a Biopharmaceutics Classification System (BCS)-based biowaiver approach (see *Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr)*. If the *in vivo* data do not cover all strengths of the product, a comprehensive scientific justification prepared in accordance with Biopharmaceutic studies - Justification for not submitting biopharmaceutic data must be provided in Module 1.11.2.

Section	Issue	Requirement
5.3.1	Generic medicine: Modified release oral dosage forms	The following studies are required: • fed and fasted • steady state study *versus* the reference modified release reference product or an appropriate scientific justification must be included in the application.
5.3.1	Generic Medicine: Clinical Usability and Safety	Generic medicines should have comparable dosage forms and identical (or a subset of) indications, directions for use and strengths in comparison with the Australian reference product's presentations. Use of different tablet sizes or excipients that are not found in the Australian reference product presentations and that have clinical implications (e.g. gluten, sodium content) should be justified and addressed by risk management initiatives (for example, relevant information or warnings on label or in PI).
5.3.1	Reports of biopharmaceutic studies using overseas reference product	For a biopharmaceutic study using an overseas reference product, the following must be provided (in accordance with Biopharmaceutic studies – Choice of the reference product for bioequivalence of generic medicines): • evidence to establish that the physical, physiochemical, qualitative and quantitative characteristics of the overseas reference product and the corresponding Australian reference product are identical • detailed validation data for the procedures used in the quantitative analysis of the excipients • data for at least two batches (including the batch used in the relevant study) from the overseas country concerned AND at least two batches from Australia.

Section	Issue	Requirement
5.3.1	New chemical entity/biological entity: Immediate release oral dosage forms	The following studies (or a robust scientific justification for not including such studies) must be submitted: • absolute bioavailability study • study to establish that the proposed formulation is optimal (e.g. a study versus an oral solution of the drug) • bioequivalence studies between the proposed registration formulation and pivotal clinical trial formulations • bioequivalence studies amongst the various strengths proposed for registration • food effect study.
5.3.1	New chemical entity/biological entity: Modified release oral dosage forms	In addition to the studies required for immediate release oral dosage forms, the following studies (or a robust scientific justification for not including such studies) must be submitted: • steady-state versus an appropriate immediate release reference product • *in vitro-in vivo* correlation studies.
5.3.1	Individual comparative bioavailability studies	• The source from which the batch of reference products was obtained must be provided. • If the batch of reference product was obtained from outside Australia, evidence that it is identical to the corresponding product distributed in Australia must be provided. • The individual calculated pharmacokinetic parameters (Tmax, Cmax, AUC, etc.) together with their means, standard deviations, etc. must be provided in tabular form. • The statistical analyses (ANOVA, estimated ratios and 90% confidence intervals for the ratios) of Cmax and AUC (and Cmin and degree of fluctuation for a steady state study) must have been carried out using parametric analyses of log-transformed data and the results reported.

Section	Issue	Requirement
5.3.1.1	New chemical entities, new routes of administration: Bioavailability study	All applications to register a new: • chemical entity • route of administration must be supported by an absolute bioavailability study (or a robust scientific justification for not including such studies). Any justification for not supplying such a study must be based on science (for example where it is not feasible to prepare an intravenous formulation or there is robust evidence to support lack of systemic absorption) and not a claimed lack of necessity.
5.3.4, 5.3.5	Pharmacodynamics and dose ranging, efficacy and safety studies	The EU guidelines relevant to the specific product, as adopted by the TGA, must be taken into account. In particular there must be: • adequate dose ranging studies to support the dose selected • an appropriate pivotal study that relates explicitly to the indication proposed • safety data that takes into account the proposed duration of use and includes information on stopping the drug.

Version history

Version	Description of change	Author	Effective date
V1.0	First version	Office of Medicines Authorisation	02/10
V2.0	Second version: Amendments to reflect consultation outcomes, changes to business rules, inclusion of specific requirements relating to sterile products, sterile drug substances and biological and improve clarity on justifications.	Office of Medicines Authorisation	05/13
V2.1	Amendments to reflect consultation outcomes regarding GMP clearance requirements at PPF lodgement and to clarify RMP formatting requirements	Office of Medicines Authorisation	04/14
V3.0	Updated	Medicines Authorisation Branch	07/15
V4.0	• Updated to include requirements for the COR report-based process and remove Category 2 application requirements. • Updated to include priority registration pathway.	Prescription Medicines Authorisation Branch/Scientific Evaluation Branch	2/18
V4.1	Administrative update to reflect reference to current legislation	Prescription Medicines Authorisation Branch	6/22

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