Australian Government

Department of Health

Therapeutic Goods Administration

Biosimilar medicines regulation

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TGA Health Safety Regulation

Contents

Biosimilar medicines regulation

This guidance assists sponsors of biosimilar medicines to complete an application to register their medicine on the Australian Register of Therapeutic Goods (ARTG) and to understand their ongoing sponsor responsibilities.

Applications for biosimilar medicines registration must meet the same requirements as for prescription medicines. Read this guidance in conjunction with our guidance on the Prescription medicines registration process.

Biosimilar medicines

A biosimilar medicine is a version of an already registered biological medicine (the reference medicine). These medicines are referred to elsewhere as:

- similar biological medicinal products (EU)
- similar biotherapeutic products (WHO)
- subsequent entry products (Canada)
- follow-on products

Both the biosimilar and its reference medicine will have the following similar characteristics (demonstrated using comprehensive comparability studies):

- physicochemical
- biological
- immunological
- efficacy and safety

Most biosimilar medicines are likely to contain biotechnology-derived proteins as the active substance(s), but this guidance also applies to other biosimilar medicines, such as those consisting of:

- vaccines
- polysaccharides, such as low molecular weight heparins

Data requirements

Before a biosimilar medicine can be registered in Australia, a number of laboratory and clinical studies need to be performed to demonstrate the comparability (biosimilarity) of the new biosimilar to the reference biological medicine already registered in Australia.

TGA has adopted a number of European guidelines that outline the quality, nonclinical and clinical data requirements specific to biosimilar medicines; and the ICH guideline on the assessment of comparability.

Quality guidelines

CHMP/437/04 Rev1: Guideline on similar biological medicinal products.

EMA/CHPM/BWP247713/2012 Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1).

Comparability guidelines

CPMP/ICH/5721/03 ICH Topic Q 5 E: Comparability of Biotechnological/Biological Products Note for Guidance on Biotechnological/Biological Products Subject to Changes in their Manufacturing Process.

Clinical and non-clinical data guidelines

EMEA/CHMP/BMWP/42832/2005 Rev 1: Guideline on similar biological medicinal products Containing Biotechnology-Derived Proteins as Active Substances: Non-Clinical and Clinical Issues. Effective 1 July 2015.

CHMP/BMWP/101695/2006: Guideline on Comparability of Biotechnology-Derived Medicinal Products after a change in the Manufacturing Process - Non-Clinical and Clinical Issues.

EMEA/CHMP/BMWP/14327/2006: Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins.

Product specific biosimilar guidelines

Product-specific biosimilar guidelines detail the clinical and safety data requirements for specific biosimilar products.

Reference medicines requirements

For a biosimilar to be registered in Australia, the reference medicine must:

- be a biological medicine that has been registered in Australia based on full quality, safety and efficacy data ('the Australian reference medicine'), and
- have been marketed in Australia for a substantial period and have a volume of marketed use so that there is likely to be a substantial body of acceptable data regarding the safety and efficacy for the approved indications

We cannot define 'a substantial period' because accumulation of an acceptable body of data depends on usage patterns of the reference medicine. Therefore, we determine 'substantial period' on a case-by-case basis and suggest you contact us to discuss this requirement for each application.

To facilitate the global development of biosimilar medicines and avoid unnecessary repetition of clinical trials, it may be possible for you, as the applicant, to compare your biosimilar in certain clinical studies and in in vivo non-clinical studies to a medicine that is not registered in Australia.

If you are using a reference medicine for your comparability studies that has not been registered in Australia, you must meet the following requirements:

- the reference medicine must be approved for general marketing by a regulatory authority with similar scientific and regulatory standards as TGA (for example, EMA or US FDA)
- a bridging study must be provided to demonstrate that the comparability studies are relevant to the Australian reference medicine (this bridging study may be abridged or

omitted if you include evidence that the medicine is manufactured in a single site for global distribution)

Many biological medicines are manufactured in multiple manufacturing sites. It may therefore be beneficial for you to select batches of reference medicine from more than one jurisdiction (for example, both the EU and the USA) in your comparability study. This ensures that the breadth of the reference medicine is appropriately represented in the comparability studies.

Related information and guidance

- Overarching biosimilar guidelines
- Product specific biosimilar guidelines
- Other guidelines relevant to biosimilars

In-house primary reference standard

Ensure you provide evidence to demonstrate that the biosimilar medicine manufacturer has established an in-house primary reference standard that is comparable to the reference medicine and the biosimilar in the comparability study.

If there are significant changes to the manufacturing process following registration, such as a major scale up of the fermentation volume, you must provide evidence to verify that the post variation product is comparable to the:

- in-house primary reference standard
- pre-variation biosimilar medicine

It is inevitable that reference and biosimilar medicines will diverge to some degree after comparability has been established. The object of the implementation of an in-house primary reference standard is to minimise this divergence.

Quality comparability studies

For comparability studies of quality aspects:

- conduct the studies according to CPMP/ICH/5721/03 ICH Topic Q 5 E guideline
- always include the in-house reference standard, reference medicine and the biosimilar medicine
- directly compare the reference standard, reference medicine and the biosimilar
- use batches of drug substance of the biosimilar medicine manufactured by a single process for both clinical trials and commercial distribution

If the biosimilar manufacturing process changes significantly due to unavoidable circumstances between clinical trial and commercial stages, then either:

- include the reference medicine in a second comparability study together with the clinical trial and commercial medicines (our preferred option)
- provide a linked comparability study showing the clinical trial and commercial medicines are similar

In either case, clearly identify the second comparability studies in the application data submitted.

Use no more than two linked bridging comparability studies, (for example, comparability of reference to clinical scale biosimilar and comparability of clinical to commercial scale biosimilar) as it is not possible to make robust comparison between the reference medicine and batches of biosimilar material made using different or evolving processes.

If direct comparison of the biosimilar and reference material is not possible (for example, if the concentration of the active substance in the reference product is too low or there are interfering excipients such as human serum albumin), extraction or concentration techniques may be used, but these must be:

- declared in the dossier
- described in full
- validated for use

Reproduction of the methodologies in a pharmacopoeial monograph is not sufficient.

The methodologies should be:

- optimised to maximise the potential for detecting differences in quality attributes
- sufficiently broad in scope to capture the full range of quality attributes
- intensive enough to fully investigate each physicochemical property or biological activity by applying orthogonal analytical techniques to evaluate the same quality attribute

Extrapolation of indications

If you intend to justify extrapolated indication[s], ensure you refer to the EMEA/CHMP/BMWP/42832/2005 Rev 1 guideline for assessing non-clinical and clinical issues in extrapolation of indications.

Current naming conventions

Trade names

Biosimilar medicines are required to have a trade name clearly distinguishable from all other products, especially the reference medicine and other biosimilar medicines.

The use of the active ingredient ABN in the trade name of a biosimilar is not acceptable.

Active ingredient names

Active ingredients of biosimilar medicines use the Australian biological name (ABN). Following a public consultation in 2017 the active ingredient of biosimilars will continue to use the ABN without a specific suffix (see proposed Australian biological name (ABN) application form).

Evaluation of application

Biosimilar medicines are evaluated through the standard prescription medicines registration process and applications need to meet the same requirements and guidelines as those for prescription medicines including:

- mandatory requirements for an effective application
- general dossier requirements
- CTD module for data requirements

CTD Module 3 of the submission will require significant modification from the EU dossier including:

- in-house standard
- bridging comparability studies
- shipping stability
- labelling

Pre-submission Planning Form

Please ensure that you select the SBMP box on the Pre-submission Planning Form.

Pre-submission meeting

We encourage you to arrange a pre-submission meeting with us to discuss proposed biosimilar application before you lodge your application.

We will not refund application and evaluation fees for biosimilars if the application is withdrawn after the first round evaluation or is found to be not biosimilar.

Product Information (PI)

Because not all biological medicines are the same, delegates approving the registration of biosimilar medicines may consider, among other things, the inclusion of the following words in Section 1 NAME OF THE MEDICINE:

> ***[Biosimilar product name]*** *is a biosimilar medicine to* ***[Reference medicine name]****. The evidence for comparability supports the use of* ***[Biosimilar product name]*** *for the listed indication[s]*

Any clinical trial information generated on the reference medicine that is reported in the reference medicine PI and included in the biosimilar PI must be clearly identified as having been produced using the reference medicine and not the biosimilar.

Further, comparative clinical trial information between the biosimilar medicine and the reference medicine should be clearly identified in Section 5.1 PHARMACODYNAMIC PROPERTIES – CLINICAL TRIALS and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

Post registration requirements

As for all newly-registered biological medicines, biosimilar medicines are risk assessed and may be placed on batch or protocol release as a condition of registration. This usually involves:

- submitting release certification and shipping records for all batches
- submitting samples from batches for release which may be tested for compliance
- applying these conditions until satisfactory batch consistency has been demonstrated (usually at least five batches of unique drug substance)

After the initial batch release phase is completed, the sponsor of the biosimilar is required to:

- submit an annual report of all batches
- provide samples to TGA for testing in periodic product surveys

Pharmacovigilance

Refer to our guidance on Pharmacovigilance responsibilities of medicine sponsors.

Risk management plans

We usually require a risk management plan (RMP) for a biosimilar medicine. Information on RMP requirements can be found in the guidance on Risk management plans for medicines and biologicals.

We will evaluate the RMP as part of the evaluation process for each biosimilar individually, considering the need for specific pharmacovigilance and risk minimisation activities on a case-by-case basis. It is likely that these activities will be consistent with those applied to the Australian reference medicine.

Adverse event reporting

When submitting adverse event reports, ensure that you clearly identify the medicine suspected to have caused the adverse event, and also provide:

- trade name of the biosimilar
- entire non-proprietary name of the biosimilar (currently, the Australian biological name)
- AUST R number
- batch number and expiry date
- dosage form and presentation

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Office of Medicine Authorisation	01/07/2013
V 2.0	Added new content identified by the word NEW following the section heading Updated content identified by the word UPDATED following the section heading	Office of Scientific Evaluation Regulatory Guidance Team	17/12/2015
V 2.1	Removed the words NEW & UPDATED added in V 2.0 Updated section 'Active ingredient names' from 'TGA proposed biosimilar naming convention' Updated hyperlinks in pharmacovigilance and risk management plan sections Editorial changes throughout to meet accessibility requirements	Scientific Evaluation branch Regulatory Guidance team	February 2018
V2.2	Updated the Product Information section to align with the headings in the new PI format	Pharmacovigilance and Special Access Branch	April 2018

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
https://www.tga.gov.au

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