Regulation of biosimilar medicines

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About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines, medical devices, blood and biologicals.
- 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, medical devices and biologicals.
- 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 <https://www.tga.gov.au>.
## Version history

<table>
<thead>
<tr>
<th>Version</th>
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</tr>
</thead>
<tbody>
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</tr>
</tbody>
</table>
Contents

Regulation of biosimilar medicines ________________ 5
Biosimilar medicines UPDATED _____________________ 5
Data requirements NEW __________________________ 5
  Quality guidelines _______________________________________________________________ 5
  Comparability guidelines _______________________________________________________ 6
  Clinical and non-clinical data guidelines ____________________________________ 6
  Product specific biosimilar guidelines _______________________________________ 6
Reference medicines ____________________________________________ 6
  Related information and guidance .................................................................--7
In-house primary reference standard UPDATED __________ 7
Quality comparability studies UPDATED __________________________ 7
Extrapolation of indications _________________________________ 8
Current naming conventions UPDATED __________________________ 8
  Trade names ________________________________________________________________ 8
  TGA proposed biosimilar naming convention _______________________________ 8
Evaluation UPDATED _________________________________________________ 9
  Pre-submission Planning Form ___________________________________________ 9
  Pre-submission meeting ____________________________________________________ 9
Product Information (PI) UPDATED __________________________ 9
Post registration requirements ________________ 10
  Pharmacovigilance UPDATED ________________________________________________ 10
  Risk management plans UPDATED ____________________________________________ 10
  Adverse event reporting NEW _______________________________________________ 10
Regulation of biosimilar medicines

This guidance seeks to assist sponsors of biosimilar medicines to complete an application to register their medicine on the ARTG while following the prescription medicines registration process and inform them of their ongoing responsibilities during the lifecycle of the medicine.

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.

The 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 UPDATED


Product specific biosimilar guidelines

Product-specific biosimilar guidelines detailing the clinical and safety data requirements.

Reference medicines UPDATED

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’).

In addition, the Australian reference medicine must 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.

It is not possible to define ‘a substantial period’ because accumulation of the body of acceptable data is dependent on usage patterns of the reference medicine and so ‘substantial period’ must be considered case-by-case. We suggest you contact us to discuss this matter for any given application.

To facilitate the global development of biosimilars 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 not registered in Australia.

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

- The reference medicine must be approved for general marketing by a regulatory authority with similar scientific and regulatory standards as the TGA (e.g. 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).

As many biological medicines are made in multiple manufacturing sites, to ensure the breath of the reference medicine is represented in the comparability studies, it may be advantageous for you to choose to use batches of reference medicine from more than one jurisdiction (e.g. both the EU and the USA) in your comparability study.

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, (e.g. 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 (e.g. 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 insufficient.

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.

**TGA proposed biosimilar naming convention**

The WHO Programme on International Nonproprietary Names (INN) are currently considering a naming convention for the active ingredients of all biological medicines, including biosimilars.

In the interim, active ingredients of biosimilar medicines will use the Australian biological name (without a specific biosimilar identifier suffix).
Evaluation **UPDATED**

Biosimilars are evaluated via the [prescription medicines registration process](#) and applications need to meet the same requirements and guidelines as those for prescription medicines including:

- **the mandatory requirements for an effective application**
- **the 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 prior to lodging the application.

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

Product Information (PI) **UPDATED**

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 under the DESCRIPTION section:

[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]

It is also important that any clinical trial information generated on the reference medicine that is reported in the reference medicine PI and included in the biosimilar PI is 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 the CLINICAL TRIALS and ADVERSE EFFECTS sections.

**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 entails:

- 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 the TGA for testing in periodic product surveys.

**Pharmacovigilance UPDATED**

Refer to our guidance on pharmacovigilance for biosimilars.

**Risk management plans UPDATED**

As for all biological medicines, sponsors must develop a comprehensive Risk Management Plan (RMP) that satisfies the general requirements outlined in: Risk Management Plans.

The RMP:

- Must outline the pharmacovigilance procedures to be implemented (as detailed in TGA adopted guidelines).
- Must specifically address immunogenicity in humans.
- Should take into account identified and potential risks associated with the reference product, as well as any risks associated with biosimilarity and predictable patterns of use, and detail how these will be addressed.
- Should include specific (routine or additional) pharmacovigilance and risk minimisation activities that are in place for the reference medicine, or provide a justification for these not being relevant for the biosimilar medicine.

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 NEW**

When submitting adverse event reports, you should ensure that you clearly identify the medicine suspected to have caused the adverse event, and also provide:
• the trade name of the biosimilar
• the entire non-proprietary name of the biosimilar (currently, the Australian biological name)
• the AUST R number
• the batch number and expiry date
• the dosage form and presentation.