Australian Government
Department of Health
Therapeutic Goods Administration

Testing of biological medicines

Applicable to biological medicines, excluding vaccines, anti-venoms and toxins

Version 2.0, July 2019

TGA Health Safety Regulation

Contents

Testing of biological medicines

This guidance applies to sponsors of biological medicines, and outlines:

- requirements of our testing program during and after registration
- how we apply a risk-based approach to prioritising our testing program

These policies and processes have been in place since 2007 and are published as part of TGA's ongoing transparency initiatives.

While the following products are included in the definition of biological medicines, this guidance does not apply to:

- vaccines
- anti-venoms
- toxins

Requirements for vaccine testing

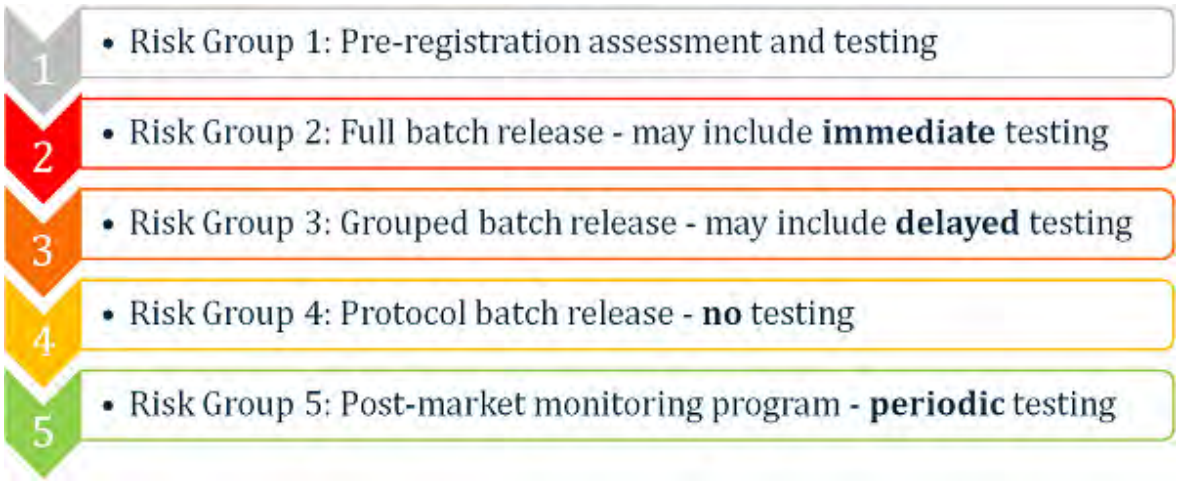
Post-registration testing of vaccines complies with internationally accepted guidelines (most recently published in Annex 2 of the WHO Technical Report Series (TRS 978) (pdf,439kb)).

Prioritising testing

Our testing program uses a risk-based strategy to prioritise testing. This allows us to focus on high risk products, while testing lower risk products less frequently, or with less labour-intensive methods. Products that have not yet established a track record of quality and safety, such as new products, and products associated with adverse drug reactions or manufacturing failures are considered high risk products.

Testing requirements based on risk level

We assign products to one of five risk groups based on the outcome of a risk assessment.



When will I know my product's risk group?

We assign the risk group once the second round of evaluation is completed. We will advise you both during and after registration of:

- the risk group for your product
- when, and if, your risk group changes

Risk Group 1: Pre-registration assessment and testing

Your product will fall into Risk Group 1 if it is a new biological medicine not currently on the ARTG.

Requirements for pre-registration assessment and testing

If your product falls into Risk Group 1, you will be required to supply us with:

- a CPD document
- pre-registration samples
- material to perform testing, including:
  - relevant reference standards
  - controls
  - cell lines
  - any other proprietary material required

Samples submitted may be unlabelled, or carry overseas labels

Testing by TGA

We take no regulatory action based on the testing results of pre-registration samples.

We may contact you to discuss the results and methodologies.

Purpose of pre-registration assessment and testing

We conduct pre-registration assessment and testing to develop and validate test methods in our laboratory, to ensure prompt and efficient batch release testing.

We may consult you regarding testing procedures during this time.

Risk Group 2: Full batch release

Your product will fall into full batch release (Risk Group 2) if it is:

- a **new** high risk biological prescription medicine
- a **variation** to the manufacturing process of already registered products, assessed as:
  - posing sufficient risk

  OR

  - deemed to be sufficiently different to the original product (e.g. transfection of a new cell-line with a different genetic construct)
- a **high risk** medicine associated with severe GMP problems, life-threatening adverse events, repeated testing failures and/or product recalls

Quarantine all batches

You must **quarantine all batches** of products on batch release until you receive an email notification from TGA releasing **each** batch for distribution.

The quarantine period for each batch depends on our testing timeframes.

Time products are on batch release

Products are generally kept on full batch release until we have confirmed batch consistency. This is usually achieved by testing at least five independent active substance batches.

After confirming batch consistency, we will:

- update the risk assessment for the medicine
- assign it to the appropriate risk category
- inform you of the changes to the conditions of registration with a section 28 letter

Urgent supply of medicines

For urgently needed products, you may request early release of your product based on the data you supplied on the understanding that:

- this approach is required because of special circumstances
- it does not set a precedent for the early release of any other products
- if subsequent testing shows non-compliance with specification, a recall of the batch may be necessary

Requirements for batch release (full and grouped)

If your product falls into either full or grouped batch release (Risk Group 2 or 3), you are required to:

- quarantine each batch
- provide us with:
  - full certificates of analysis of the **drug product** and **active substance** batches

- evidence of maintenance of approved temperature storage conditions during shipment to Australia for the drug product
- samples of the drug product
- material to perform testing, including:
  - relevant reference standards
  - controls
  - cell lines
  - any other proprietary material required.

In some cases, we may also require you to send raw data for specified assays, including:

- gel photographs
- chromatography traces
- statistical analysis

Samples of the drug product

You are to provide us with batches of drug product from different, independently manufactured, active substance batches. This means:

- when drug product batches are made from the same active substance batch, you only need to provide samples for the first drug product batch
- for subsequent batches of drug product from the same active substance batch, you only need to supply:
  - a statement detailing the active substance identity
  - the certificate of analysis of the drug product batch(s)
  - evidence of maintenance of the approved temperature storage conditions during shipment

Submitting the requested material to TGA

Send all required materials with sufficient lead-time to allow for the appropriate testing. New products require at least two months lead time due to the need to develop and validate new test methods. Established products require two weeks lead time as they have established test methods.

Email us to make arrangements for the delivery of the requested items and to send the relevant documentation.

Under the appropriate storage conditions, send samples and materials required to:

Therapeutic Goods Administration
Laboratories Branch, Biochemistry Section
136 Narrabundah Lane
Symonston ACT 2906

Testing by TGA

We assess the submitted data and test the samples as quickly as possible to ensure you can distribute your product as soon as possible. Our testing timeframes vary.

To reduce testing timeframes, we recommend you notify us prior to sending samples so we can schedule testing at the earliest opportunity.

Testing timeframes

Our testing time varies depending on the tests involved, for example:

- *in vivo* assays may take several weeks
- a single physicochemical test may only take 5 working days

Testing results

We publish a summary of all TGA test results twice a year on our database of TGA Laboratory testing results.

We deal with any excursions from specification in consultation with you and, if necessary, other Branches of the TGA. In such cases:

- we will contact you to negotiate the outcome
- you will not be granted permission to distribute the product in Australia until all issues are resolved.

We inform you of our test results in a test report letter.

More information is provided in test methods and handling of results.

Purpose of full batch release

We place products on full batch release (Risk Group 2) to:

- demonstrate manufacturing consistency of new or significantly changed medicines

OR

- monitor demonstrably high risk medicines

Risk Group 3: Grouped batch release

Your product will fall into Grouped batch release (Risk Group 3) if it is:

- a **new** medium risk biological prescription medicine
- a **variation** to the manufacturing process of already registered products, if we assess the variation as:
  - posing sufficient risk

  OR

  - deemed to be sufficiently different to the original product (e.g. major change to fermentation conditions like the use of serum-free medium)
- a **medium risk** medicine associated with moderate GMP problems, health-threatening adverse events, repeated testing failures and/or product recalls

Quarantine all batches

You must **quarantine all batches** of products on batch release until you receive an email notification from TGA releasing **each** batch for distribution.

The time a product is on grouped batch release is the same as for products on full batch release (Risk Groups 2).

Requirements for grouped batch release

For products on grouped batch release:

- the requirements are the same as for products on full batch release (Risk Groups 2)

However:

- we will grant permission for you to release your product based on review of the certificates of analysis provided
- you are not required to wait for the completion of our testing

Testing by TGA

For products on grouped batch release, we perform delayed testing.

Samples are:

- stored appropriately until we have a sufficient quantity
- tested together for efficiency

Testing results

We inform you of our test results in a test report letter.

We publish a summary of all TGA test results twice a year on our database of TGA Laboratory testing results.

We deal with any excursions from specification in consultation with you and, if necessary, other Branches of the TGA. In such cases:

- we will contact you to negotiate the outcome
- if the failure is a critical quality attribute, you will probably be required to recall the product

More information is provided in test methods and handling of results.

Purpose of grouped batch release

We place products on grouped batch release (Risk Group 3) to:

- demonstrate manufacturing consistency of new or significantly changed medicines

OR

- monitor medium risk medicines

We process products on grouped batch release (Risk Group 3) to:

- allow rapid release for new medium-risked products
- economise on testing resources

Risk Group 4: Protocol batch release

Your product will fall into Protocol batch release (Risk Group 4) if it is:

- a **new low** risk biological prescription medicine
- a **new low to medium** risk biological prescription medicine from a manufacturer with an established testing consistency record from other biological medicines
- a **variation** to the manufacturing process of already registered products, if we assess the variation as:
  - posing sufficient risk

  OR

  - deemed to be sufficiently different to the original product (e.g. implementation of more stringent test specifications for critical quality attributes)
- a **low risk** medicine associated with moderate GMP problems, health-threatening adverse events, repeated testing failures and/or product recalls

Quarantine all batches

You must **quarantine all batches** of products on batch release until you receive an email notification from TGA releasing **each** batch for distribution.

Time products are on protocol batch release

For **new low risk** products, monitoring continues until consistency has been demonstrated (usually 5 independent active substance batches).

For products with **identified problems**, monitoring may continue until there is adequate resolution, even where:

- ongoing batch release testing is completed

AND

- the analytical data have been demonstrated as reliable

Once all problems have been resolved, we will email you a letter changing the conditions of registration under section 28 of the Act.

Requirements for protocol batch release

If your product falls into protocol batch release (Risk Group 4), you are required to provide us:

- full certificates of analysis of the drug product and, where specifically requested, active substance batches
- evidence that approved temperature storage conditions have been maintained during shipment to Australia

Timeframes for protocol review

We will usually assess the data and notify you of the outcome within 5 working days.

Purpose of protocol batch release

We place products on protocol batch release to:

- monitor new low risk products to:
  - demonstrate batch consistency
  - ensure shipping conditions are maintained with minimal interruption to supply
- monitor products that may have significant, but not severe, problems with:
  - GMP
  - adverse events
  - repeated testing failures and/or product recalls

Any issues for products on protocol batch release do not warrant testing of samples, such as:

- recalls for labelling problems which **don't** affect the quality or safety of the product
- when significant manufacturing problems have been reported but adequate corrective actions have been taken

Risk Group 5: Post-market monitoring program

Your product will fall into our post-market monitoring program if it:

- is a relatively low risk
- has demonstrated batch consistency and good compliance

Requirements for our post-market monitoring program

If your product falls into the post-market monitoring program, we require you to:

- submit annual product reports
- participate in periodic product surveys

Annual product report for biological prescription medicines

You are required to complete an annual product report for biological prescription medicines. We use information in the annual report to update information in the risk assessment tool.

The annual product report requests, for that year:

- the number of batches, and units, distributed
- the number of deviations from approved storage conditions, during shipping (see Temperature excursions of biological medicines)
- deviation reports for all unapproved temperature excursions

Under GMP requirements, you are expected to have immediate access to all batch data and deviation reports or justifications. If you submit inadequate deviation reports, we may request more information. Deviations should be relatively few in a well-controlled QA system.

Deadline for submitting annual product reports

You are able to negotiate the submission date by emailing us.

Product surveys

We attempt to test all biological medicines on the market at regular intervals. We calculate the testing intervals using our risk assessment tool.

Requirements

For our product surveys, when requested, you are required to provide:

- samples of the drug product
- material to perform testing, including:
  - relevant reference standards
  - controls
  - cell lines
  - any other proprietary material required

Our approach

During a product survey, we request samples from all sponsors marketing products:

- with similar active substances

OR

- used for similar indications

For example, we would request samples from suppliers of:

- all insulin preparations (whether short or long acting)
- all erythropoiesis stimulating agents (even though the active substances are different)

Testing by TGA

We inform you of our test results in a test report letter.

We publish a summary of all TGA test results twice a year on our database of TGA Laboratory testing results.

We deal with any excursions from specification in consultation with you and, if necessary, other Branches of the TGA.

Purpose of our post-market monitoring program

We attempt to test all biological medicines on the market (at regular intervals) using a risk-based prioritisation. The interval is calculated in the risk assessment tool from the inherent risk of the product.

Periodic risk assessments and changes to risk group

We initiate a risk assessment once the second round of evaluation is completed. For most biological medicines, the risk assessment results in full, grouped or protocol batch release.

We update the risk assessment once:

- batch consistency is demonstrated

AND

- the batch release period is ended by a change of conditions of registration, under section 28 of the Act

After demonstrating batch consistency, we generally assign products to the post-market monitoring program (risk group 5). From that time, we update the risk assessment on a regular basis (usually every three years).

Impact of significant or severe problems on the assigned risk group

We may review and update our risk assessment if there are local or overseas reports of significant or severe problems with:

- GMP
- adverse events
- repeated testing failures and/or product recalls

Events that may result in a risk assessment review may include situations where there are reports of life threatening adverse events or immunogenic reactions.

Changes to risk group

If the risk assessment tool identifies a change in the risk of the product, this may trigger a recommendation to change the risk group.

We will consider any mitigating or exacerbating factors (in consultation with the sponsor), before assigning the product to an appropriate risk group.

If this risk group is different to the current risk group of the product, we will vary the conditions of registration (under section 28 of the Act) and inform the sponsor by email.

Test methods and handling of results

We inform you of our test results in a test report letter.

We publish a summary of all TGA test results twice a year on our database of TGA Laboratory testing results.

TGA test methods

For testing biological medicines, we are increasingly using validated TGA in-house orthogonal screening techniques. We apply internal acceptance criteria based on either:

- the most stringent

OR

- the mean or median

from approved specifications of the tested group of biological medicines

Results of testing

Products whose results are:

- within screening acceptance criteria are reported as passing
- outside, or close to, the screening acceptance criteria are retested

Retesting methods

In re-testing samples, which do not meet TGA in-house screening acceptance criteria, we use:

- pharmacopoeial methodologies where available, however we will apply the approved specifications if they differ from the pharmacopoeial standards

OR

- methodologies and specifications detailed in the Certified Product Details (CPD), where pharmacopoeial methods aren't available

Retest results

If non-compliance is confirmed using compendial or CPD methods, we will inform you and negotiate an appropriate course of action:

- for **marginal failures** or for **failures in non-critical quality attributes**, this may be:
  - a simple information letter
  - a warning
  - a possible request for further samples (for testing)
- for **significant failures to critical quality attributes** or **failures which may have safety implications**:
  - the batch may be recalled
  - you may be required to send 'Dear Doctor' letters
- **if you disagree with our test results**, you may nominate a third party to carry out additional testing

Validating or verifying a method for TGA use

Before we use any method, we validate or verify their use according to the following standards:

- Current Good Manufacturing Practice for Finished Pharmaceuticals, section 194 (a)(2), US Code of Federal Regulation - Part 211
- General Requirements For The Competence Of Testing And Calibration Laboratories, ISO/IEC 17025, Part 5.4.2
- Validation and Verification of Quantitative and Qualitative Test Methods, NATA General Accreditation Guidance – 14 January 2018
- Validation of Analytical Procedures: Text and Methodology Q2(R1), ICH Harmonised Tripartite Guideline.

Screening and CPD methods may require standards and internal controls, which only the manufacturer can supply. Such reagents may need to be verified before use in batch release. In such cases, after completion of the second round of evaluation, we may request:

- a CPD document
- pre-registration samples
- standards
- consumables

Certified Product Details (CPD)

The Certified Product Details (CPD) of a biological medicine specifies its:

- formulation
- manufacturing process
- test methods
- specifications

When a new biological medicine is registered, ensure you provide us with an electronic draft of the CPD, as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines.

A template to prepare a CPD is available on our website.

Once drafted, send your CPD as a **single pdf document** to us. You can also use this address as a first point-of-contact on any testing issue.

Approved changes to existing ARTG entries

When we have approved a change to an existing ARTG entry, either through a category 3 application or a self-assessable change, ensure you provide an updated CPD to the:

- active substance
- product specifications and/or test methods

Treatment of confidential information

As laboratory protocols and reference standards may be subject to intellectual property protection, we treat all information supplied in the CPD as official information as detailed in Treatment of information provided to the TGA.

Temperature excursions

Deviations from approved storage conditions may cause a biological medicine to be of unacceptable quality and therefore not suitable for supply.

There are ways you can gain permanent approval of temperature excursions (of specified and validated magnitude and duration) to allow you to manage them under GMP. See Temperature excursions of biological medicines.

Risk assessment tool for biological medicines

To assess the potential risks posed by a therapeutic good objectively, we use an internal risk assessment tool to address:

- consequences, which are inherent risks in the product and its use
- likelihood, which are risks posed by manufacturing, distribution and marketing

Post-market monitoring program – determining time intervals

The risk assessment tool is also used to assign:

- testing intervals for the post-market monitoring program
- risk assessment intervals for reviewing a product's risk rating

Evaluations and initial risk groups

During the evaluation process, we assign your biological medicine to a risk group using the risk assessment tool.

Your application to register a new biological medicine is:

- managed through the prescription medicines registration process
- submitted using the electronic submission process
- assigned a risk group during the course of evaluation

Variations to prescription medicines - excluding variations requiring evaluation of clinical or bioequivalence data: Process guidance outlines the normal Category 3 and self-assessable notification processes.

Impact of significant manufacturing changes on the assigned risk group

If you have a significant change in a manufacturing process, you are required to complete a comparability study before and after the change.

We will review the assigned risk group and notify you if any change is required, such as to:

- the assigned risk group, which may increase if the risk level is increased
- your release procedures, if the new risk group requires batch or protocol release

Changes to test methods or specifications

If you make changes to testing methods or specifications you will need to submit an updated copy of the Certified Product Details document to us.

Requirements for batch or protocol release

We assess the requirements for batch or protocol release testing during the evaluation process. The Delegate considers all recommendations and their suitability for inclusion in the approval letter.

Additional information which may be requested

If test methods used in the analysis of a new biological medicine are complex and approval seems imminent after the second round of evaluation, we may request:

- a Certified Product Details (CPD) document
- pre-registration samples, standards and consumables for method development

Legislative basis

Evaluation and registration of all new biological medicines:

- section 25 of the *Therapeutic Goods Act 1989* (the Act)
- with reference to subregulations 16C and 16D of the *Therapeutic Goods Regulations 1990* (the Regulations)

Variation of the entry of the ARTG:

- section 9D of the Act

Conditions of registration:

- section 28 of the Act

Testing of therapeutic goods:

- Part 5 of *Therapeutic Goods Regulations 1990*

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	TGA	22/12/2015
V2.0	Original document re-formatted and updated to reflect the latest practices, introducing information on use of TGA in-house orthogonal testing methods.	Biochemistry Section Regulatory Guidance Team	July 2019

Therapeutic Goods Administration

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