Australian Government
Department of Health
Therapeutic Goods Administration

Quality for listed medicines

Australian regulatory guidance

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TGA Health Safety Regulation

Contents

Introduction

The *Therapeutic Goods Act 1989* (the Act) requires that all applicants wishing to list a medicine must certify that they hold the relevant documentation to substantiate the safety, quality and efficacy of the goods for the purposes for which they are to be used.

Applicants of all listed medicines are required to certify that their medicine complies with applicable manufacturing requirements- Listing a medicine in the ARTG in General guidance for listed medicines.

Some listed medicines comprise relatively simple ingredients (for example: amino acids, mineral salts, vitamins) and the quality parameters applying to such products are essentially the same as for other medicines. Special considerations are required for those listed medicines that contain complex ingredients, that are difficult to characterise, and/or certain combinations of multiple active ingredients.

This guidance describes the information regarding the quality of the product that should be held by listed medicine applicants.

Guidelines on quality for listed medicines

There are a number of scientific guidelines of particular relevance to listed medicines:

- Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products (CPMP/QWP/122/02, rev 1).
- Quality of Herbal Medicinal Products/Traditional Herbal Medicinal Products (CPMP/QWP/2819/00 Rev. 2) provides guidance to achieve consistent quality for products of herbal origin. Note herbal ingredients included in listed medicines must meet the definition of a herbal substance.
- Test procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products/Traditional Herbal Medicinal Products CPMP/QWP/2820/00 Rev. 2) provides general principles for setting and justification of a uniform set of specifications for products of herbal origin.

Sponsors and potential applicants should also be aware of the following documents that provide specific guidance for complementary medicines:

- Annex 7 of the Guide to good manufacturing practice for medicinal products provides specific guidance on the manufacture of herbal medicinal products.
- Supplier assessment, approval and qualification for listed and complementary medicines provides the steps by which supplier qualification may be achieved.
- Identification of herbal materials and extracts provides common questions and answers relating to identification of herbal materials.
- Sampling and testing for listed and complementary medicines covers the sampling and testing requirements for raw materials used in the manufacture of intermediate, bulk or finished complementary medicinal products. It also describes a plan for reduced sampling and testing once an approved supplier has been qualified.
- Starting material analytical procedure validation for complementary medicines describes the minimum approach acceptable to achieve validation of the test procedures used for starting materials for use in complementary medicines.
- Finished Product Specifications and certificate of analysis.

- Equivalence of herbal extracts in complementary medicines assists sponsors of medicines containing herbal extracts to determine how and when a herbal extract may be considered 'equivalent' to an ingredient currently included in a therapeutic good and when it may be used as a substitute without causing the product to be considered a different therapeutic good.
- Use of modified unprocessed herbal materials in complementary medicines assists sponsors in identifying situations where the composition of an unprocessed herbal material has been modified to the extent that it is significantly different from the original material approved for use in listed or registered medicines.
- Ongoing stability testing for listed and complementary medicines provides guidance on the development of a stability testing protocol for listed and complementary medicines. The approach taken by TGA in relation to stability testing of herbal and certain other listed complementary medicines recognises the differences between these types of therapeutic products and pharmaceutical products that usually contain a single, chemically defined, active ingredient.
- Stability testing of listed complementary medicines provides common questions and answers on stability testing.
- Product quality reviews (PQRs) for listed and complementary medicines provides guidance on product quality reviews, which are part of GMP requirements.
- Process validation for listed and complementary medicines provides guidance to ensure that the validation process used is effective in producing a quality medicinal product.
- Consistent with the TGA's risk-based approach to the regulation of medicines, it may be possible to justify certain situations where it is not necessary to assay an ingredient in every batch of finished product. In such situations, the content of an ingredient, or a component within the ingredient, may be estimated from the amount dispensed during the manufacture of the product. This practice is termed 'quantified by input' (QBI). However, based on risk to consumers, it is not appropriate to apply this practice to all ingredients—refer to Use of the term 'quantified by input' for listed complementary medicines for more information.

Sponsors and potential applicants should also be aware of information on 'Allowed changes to the nominal amounts of certain excipients', included in CTD modules 2, 3, 4 and 5 for registered complementary medicine applications- which is also relevant for listed medicines.

Finished product specifications and certificates of analysis

Finished product specifications

The finished product specification is the set of tests and limits applicable to the finished medicinal product to ensure that every batch is of satisfactory and consistent quality at release and throughout its shelf life. The specifications should include all critical parameters in which variations would be likely to affect the safety or efficacy of the product, for example: assay.

The specifications against which a finished product is tested before release for sale are referred to as the 'batch-release specifications'. The specifications against which a finished product is tested to ensure satisfactory quality throughout its shelf life are referred to as the 'expiry specifications' or 'end-of-shelf-life specifications'. The product, if tested at any time within its shelf life, must comply with the requirements in the expiry specifications.

Test procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products / Traditional Herbal Medicinal Products CPMP/QWP/2820/00 Rev. 2 provides general principles for setting and justification of a uniform set of specifications for finished products containing ingredient(s) of herbal origin.

Specifications should also take into account Australian legislative requirements for finished products.

The standards recognised under the *Therapeutic Goods Act 1989* are those made by the Minister under section 10 of the Act (therapeutic goods orders) and the default standards, which currently are relevant statements in monographs in any of the following: *British Pharmacopoeia* (BP), *European Pharmacopoeia* (Ph. Eur.) or the *United States Pharmacopeia – National Formulary* (USP). It should be noted that any matter specified in an order under section 10 of the Act has precedence over requirements of the default standards.

The general monographs of the BP, Ph. Eur. and USP are also relevant, for example: the BP monographs 'Herbal Drugs', 'Herbal Drug Preparations' and 'Extracts'.

The most recent edition of the cited pharmacopoeia should be used.

Where a finished product does not comply with Australian legislative requirements, consent to supply the product is required—refer to Consent to import, supply or export therapeutic goods that do not comply with standards - information for industry

Information required for a finished product specification

Product details

- name of product
- product code
- date of specification
- revision or version number
- a table listing the tests performed, the expiry requirements or acceptance criteria for the tests (and where different, the release requirements) and reference to the test method (for example: BP HPLC method, 'in-house' TLC method). The tests performed should include the following:
  - appearance of the product [note that the requirements should include: a description of the type of dosage form and any special characteristics (for example: modified release)]
  - physical tests including: average weight, uniformity of weight/ content, disintegration/dissolution (where relevant)
  - chemical tests, including: identification, assay, related substances (where relevant)
  - the microbiological tests
  - any other tests

- a statement of whether all the tests are performed on each batch of finished product; and if not, what tests are performed on rotation and the frequency.

Certificate of analysis for finished products

A certificate of analysis (used for 'release for supply' purposes) is a document certified as a truthful statement of the tests and test results for an individual, manufactured batch of a particular finished product.

Information required for a certificate of analysis

- the manufacturer
- the product name
- the batch number of the product
- the date of manufacture of the batch, the date of the testing and the date of the certificate
- the tests, the tests results, acceptance criteria and a reference to each test method
- the signature of the appropriate company official.

'Quantified by input' for listed medicines

If a manufacturer of a listed medicine meets certain criteria, they may not be required to assay an ingredient in a finished product. The guidance also provides wording that a manufacturer could use on a certificate where an ingredient has been *'Quantified by input'* (QBI). Please note that the guidance provided in this document does not override or replace the need to comply with all relevant statutory requirements, nor affect the legal obligations of the medicine's sponsor who is ultimately responsible.

It is intended that this guidance be used by manufacturers, in consultation with the relevant sponsor, as part of product development. It is most relevant where a quantitative claim (see note 1) is made for a particular active ingredient in a listed medicine. However, in certain circumstances, these principles may also be applied to other ingredients or components, including those that are considered to be 'restricted ingredients' (see note 2).

Under good manufacturing practice (GMP), it is a requirement that all active ingredients in medicines be tested to confirm that the content complies with prescribed standards. However, it is recognised that in some circumstances this may not be possible or practical to achieve. Where it is established that such medicines are manufactured in accordance with the principles of the Australian adopted Manufacturing principles for medicinal products and other criteria are met, quantitative testing of the active ingredient in the finished product may be omitted and the ingredient in the product can be 'QBI'. However, based on risk to consumers, it is not appropriate to apply this practice to all ingredients.

If certain specific testing of a listed medicine is not going to be performed, it is important that all other aspects of its manufacture are performed under appropriate GMP. That is, if the finished product is not fully tested, testing of the raw materials becomes more critical. In addition, if there are quantity-based restrictions that affect the medicine's eligibility for listing in the Australian Register of Therapeutic Goods (ARTG), careful consideration needs to be given as to whether reduced testing of the finished product is appropriate.

Where a manufacturer does not intend to assay an active ingredient, or a restricted ingredient or component, in a batch of a listed medicine, this decision must be supported by written

justification. The justification may be reviewed at a Therapeutic Goods Administration (TGA) GMP inspection of the manufacturer or by the TGA during a listing compliance review.

Assessing the suitability of QBI for a listed medicine

When determining whether the content of an active ingredient or restricted ingredient/component in a listed medicine could be QBI, the following points need to be addressed:

- any quantitative claims made for the ingredient in the finished product
- any restrictions applicable to the ingredient or any component in the ingredient: these can relate to scheduling entries in the Poisons Standard (see note 3), or be identified in the Permissible Ingredients Determination
- critical testing of the active raw material, in accordance with GMP principles
- the availability of a validated assay method for the ingredient/component in the finished product
- whether QBI would be applied to all batches or only certain batches (testing would be done on a rotational basis).

Complex active ingredients

Many ingredients of biological origin used in listed medicines are not single component ingredients, for example: shark cartilage or non-standardised herbal extracts. In these situations, where the ingredient/component is not subject to any restrictions and no associated quantitative claims are made in the finished product, the ingredient may be QBI. The words 'Not assayed, quantified by input', or words to that effect, may be used on the certificate of analysis of the finished product.

Simple ingredients and components of ingredients

In cases where the active ingredient consists of a single component, or where a quantitative claim is made for any component within an ingredient, it is usually expected that the ingredient/component would be assayed in the finished product. This is particularly important when, to ensure the safety of the medicine, an ingredient/ component is subject to restrictions in any relevant legislative instrument.

However, in certain situations it may be justifiable to QBI such ingredient/components, including those that are restricted, and not assay the finished product. This could occur as part of a rotational testing program (see note 4 under Additional notes for QBI, below) where, for certain batches of medicine, the assay of a specified ingredient/component would not be performed. In these cases, a statement such as: *'Quantified by input. This ingredient is part of a rotational testing program and was not assayed in this batch'* may be used on the certificate of analysis of the finished product. In some instances, a validated limit test for simple ingredients or components (see note 5 under Additional notes for QBI, below)) may be able to be used as part of a QBI justification. The use of such a test may provide an acceptable level of assurance that the ingredient/component is below the level which would affect the eligibility of the medicine for listing.

QBI justifications

Difficulties with testing methodologies may be the justification for using QBI for an active ingredient. For example, the formulation of the medicine may be of such complexity that a validated assay method for the ingredient in the finished product is unavailable or is difficult to achieve. To be able to apply the principles of QBI to the manufacture of these medicines, the potency of the ingredient/component must have been established according to the Manufacturing principles for medicinal products prior to inclusion in the formulation. Once this has been done, the words *'Not assayed. Quantified by input'* may be used for the ingredient/component on the certificate of analysis of the finished product.

For multi-active medicines (for example: multivitamin/mineral complexes) it may be justifiable to use QBI for ingredients for which a validated assay method for testing the finished product is available. If the quality and safety of the medicine is assured through other testing, the assay of certain ingredients may be put on a rotational testing program. Again, this can only be applied if the potency of the ingredient/component has been established according to the Manufacturing principles for medicinal products prior to inclusion in the formulation. Once this has been done, the words '*Not assayed, quantified by input*' or '*Quantified by input. This ingredient is part of a rotational testing program and was not assayed in this batch*' may be used for the ingredient/component on the certificate of analysis of the finished product.

Implementation

Consistent with the principles and guidance in this document, some testing must be performed on each batch of the finished product where a quantitative claim is made on the label. That is, there must be sufficient testing to provide assurance that the product is of intended quality.

Additional notes on QBI

Note 1: A 'quantitative claim' is a claim made for a medicine that states that a particular quantity of an ingredient, or component in an ingredient, is present in the medicine.

Note 2: An ingredient, or component within an ingredient, is considered to be 'restricted' where there is a quantity or concentration based restriction referred to in a legislative instrument, such as the Permissible Ingredients Determination (see definition of 'restricted ingredient' below).

> 11(2) A substance is a restricted ingredient if:
> (a) it is an ingredient in a relevant medicine; and
> (b) for that medicine to be, or to remain, eligible for listing, the permissible quantity or concentration of the substance in the medicine is restricted by operation of any of the following:
> (i) Schedule 4;
> (ii) the Poisons Standard;
> (iii) a condition imposed under section 28 of the Act;
> (iv) a standard under section 10 of the Act;
> (v) the Required Advisory Statements for Medicine Labels document;
> (vi)any other provision in these Regulations or in the Act that deals with eligibility of medicines for listing.
> 11(3) In this regulation:
> relevant medicine means a medicine that is listable goods or listed goods and that is not an export only medicine.

Where a quantity-based restriction may apply to an ingredient or component, it is generally not appropriate for that ingredient to be QBI because of the on-going need to confirm that

the medicine meets the quantity-based restriction and remains safe. This means that any ingredient referred to or mentioned in any of the legislative instruments may generally not be QBI. However, there may be circumstances where, for example, the restriction applies to a component within an ingredient and it can be demonstrated that the concentration is appropriately controlled in the raw material. In these instances, it is possible to apply the principles of QBI and not assay the restricted component in the finished product. Further, if the concentration is significantly below the restricted level, an appropriate limit test could be used on the raw material.

Note 3: A substance may be 'referred' to or mentioned in the Poisons Standard, but it may not be 'included' in a Schedule. That is, it may not be subject to the requirement of the Poisons Standard entry because the quantity/concentration of the ingredient is below that specified in the entry. It should be noted that, by definition, a listed medicine cannot contain any substance that is included in a Schedule. For example: vitamin D preparations are referred to in the Poisons Standard for internal human therapeutic use, although preparations containing 25 micrograms or less of vitamin D per recommended daily dose are not subject to restrictions in the Poisons Standard. Therefore:

- medicines that contain vitamin D at levels that provide a daily dose of more than 25 micrograms are included in Schedule 4 and cannot be used in listed medicines
- for listed medicines that provide 25 micrograms or less of vitamin D, a vitamin D assay of the finished product must be performed.

In instances where reference to an ingredient in a legislative instrument only relates to a requirement for a warning statement (for example: *Hypericum perforatum* in the Permissible Ingredients Determination) that ingredient may, subject to the principles of this document, be eligible for quantification by input. Please note that this would not be the case if the warning statements are quantity dependent.

Note 4: Rotational testing is the performance of specified tests on pre-selected batches and/or at predetermined intervals, rather than on a batch-to-batch basis with the understanding that those batches not fully tested must still meet all acceptance criteria established for that product. This represents a less-than-full schedule of testing and should be supported by written justification. This justification may be reviewed at a TGA GMP inspection of the manufacturer or by the Complementary and OTC Medicines Branch (COMB).

Note 5: A 'limit test' is a semi-quantitative assay for a component in a product. It generally provides a pass/fail result for the component. It should be developed with suitable specificity, precision and accuracy, but it is not expected to provide an exact value.

The use of a validated limit test may provide an acceptable level of assurance that a particular ingredient or component is present in a product at levels consistent with low risk and, subject to the principles of this document, be eligible for QBI. In instances where restrictions in the Poisons Standard or in the Permissible Ingredients Determination apply to an amount of an ingredient/component in a recommended daily dose, the application of a limit test will require knowledge of the recommended dose. In instances where this is not known, manufacturers should liaise with the product's sponsor to ascertain this information.

Requirements for specific ingredients

Table 1outlines requirements for specific types of ingredients in listed medicines.

Table 1: Requirement for specific types of ingredients

Ingredient	Requirement
Incidental minor excipients in listed medicines	Incidental minor excipients (IME) are substances that are added to certain raw material ingredients during the manufacture of that ingredient, for the purpose of increasing its stability, extending shelf-life or improving physical properties. IME are themselves substances that are approved for use in listed medicines and are present in the raw material at levels such that their concentration in the finished medicine is insignificant. **Note: an ingredient that is subject to any restriction or is required to be declared cannot be considered as an incidental minor excipient.** The TGA currently recognise specific instances where an IME included in the raw material may vary, for example: • minor changes required to the type of anti-oxidant used in the manufacture of different batches of some oil raw material ingredients, such as fish oil • the possible presence of silicon dioxide when used as an anti-caking agent in some ingredients. In the above cases, the anti-oxidant or silicon dioxide ingredients are considered to be IME and applicants are not required to disclose details of these substances (used in the manufacture of an ingredient) in the listing application (for a medicine whose formulation includes that ingredient). We will give consideration to recognising other IMEs if suitable justification is provided. Please contact complementary.medicines@health.gov.au for such enquiries.
Requirements/ limits for proprietary ingredients	All ingredients included in the proprietary ingredient's formulation must be permitted for use in listed medicine. If an ingredient in the proprietary ingredient formulation is not permitted for use in listed medicines, then: • the ingredient must be evaluated as a new substance for use in listed medicines (see Applications for new substances in listed medicines); or • the safety of the ingredient must be established as part of the evaluation process for a registered medicine. The following limits apply to the total concentration allowed in listed medicines for proprietary ingredients that are flavours, fragrances and inks (colourings): • Flavours 5% • Fragrances 1% • Inks 0.1% The colourings contained in proprietary ingredients used in listed medicines are required to be only colourings used in medicines for topical and oral use.

Ingredient	Requirement
	The specifications applied to proprietary ingredients should be appropriate for the nature of the ingredient, and for its function and proportion in the finished product. For a proprietary ingredient formulation that contains an active ingredient (active pre-mix), specifications must include tests for the identification and content of the active ingredient and impurity tests. For further information on proprietary ingredients refer to: • Notification of a new proprietary ingredient. • Manufacturing requirements for proprietary ingredients in Overview of the regulation of listed medicines and registered complementary medicines • Supplier assessment, approval and qualification for listed and complementary medicines. If a medicine includes a proprietary ingredient and the medicine label includes a negative disclosure statement (for example: 'sugar free'), sponsors must ensure that the substance referred to in the negative disclosure statement is not contained in any proprietary ingredient in the product formulation. The onus is on the sponsor to obtain this assurance from the supplier.
Vitamin and minerals	Vitamin or mineral supplementation indications are only permitted where the recommended daily dose of the product provides at least 25% of the Australian Recommended Dietary Intake (RDI) for that vitamin or mineral. If there is no Australian RDI for a vitamin or mineral, an RDI from another country may be used. For information on evidence requirements for vitamin and mineral indications included in Evidence Guidelines for listed medicines

Version history

Version	Description of change	Author	Effective date
V1.0	Information extracted from ARGCM v 8.0 for original publication as below: • Information on quality taken from pages 54 to 60 of ARGCM V8.0. • Information on requirements for specific ingredients taken from pages 23 and 24 of ARGCM v8.0 and compiled into a table. Revised introductory paragraph. Information on proprietary ingredients clarified and a link provided to Supplier assessment, approval and qualification for listed and complementary medicines.	Complementary & OTC Medicine Branch	May 2020

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