Australian Government

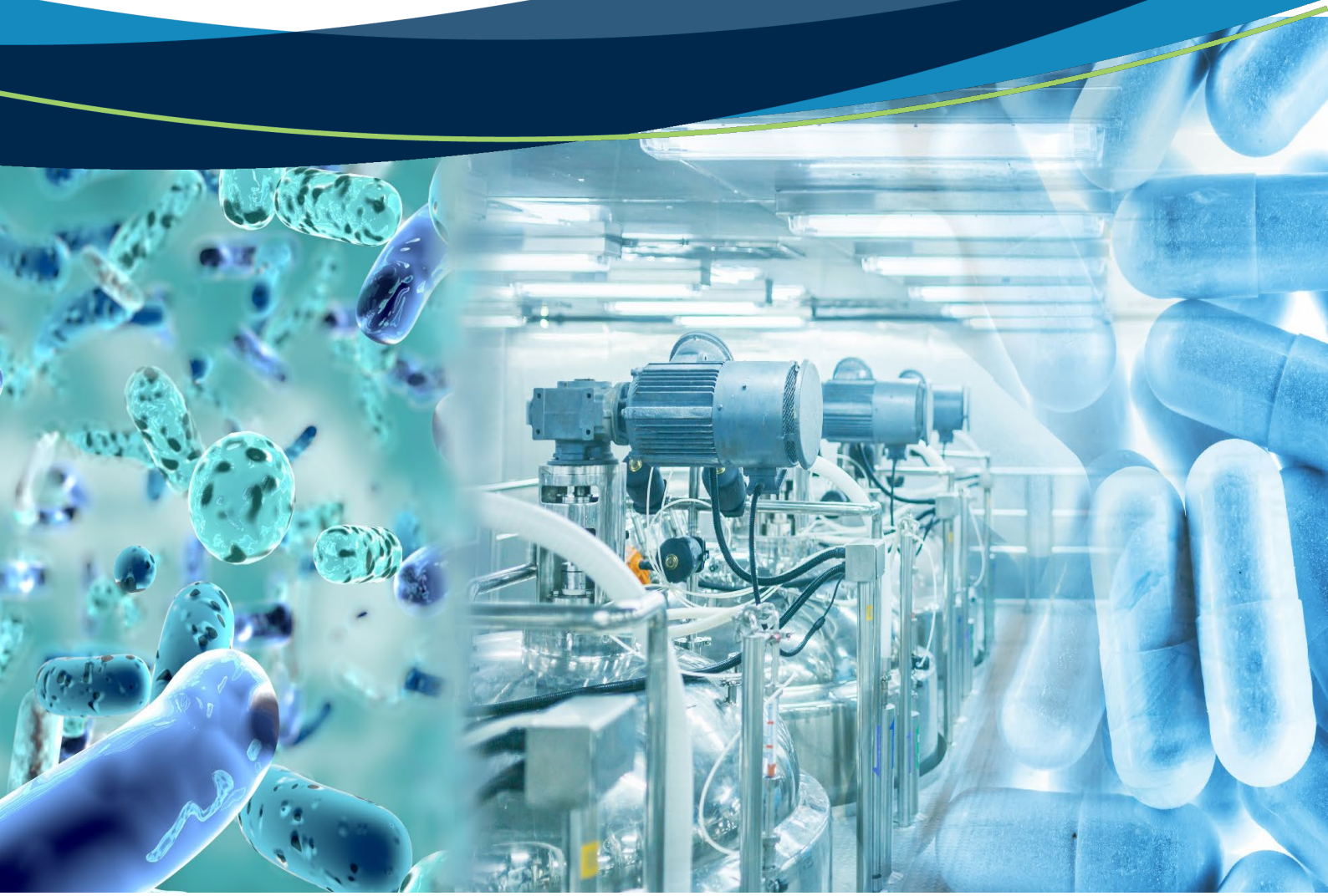
Department of Health and Aged Care

Therapeutic Goods Administration

Guidelines for the Quality of Listed Probiotic Medicines

Version 1.0, Month Year

TGA Health Safety Regulation



1 Purpose

The purpose of these Guidelines is to help sponsors and manufacturers meet the technical, scientific and regulatory requirements to ensure the quality of their probiotic medicine is acceptable under the *Therapeutic Goods Act 1989* (the **Act**).

2 Scope

These Guidelines apply to probiotic medicines (with an AUST L or L(A) number) that are **listed** on the Australian Register of Therapeutic Goods (ARTG). Probiotics are defined as live microorganisms that when administered in adequate amounts, are proposed to confer a health benefit on the host.

Where these Guidelines provide interpretations of legislation, these are not mandatory requirements but provide transparency to industry by showing sponsors what a TGA delegate considers when assessing the quality of listed and assessed listed probiotics in a compliance review. Additionally, these Guidelines are intended to assist with sponsor and manufacturer compliance by naming and explaining the most relevant applicable legislation related to ensuring the quality of probiotic medicines.

These Guidelines reference, state and summarise legislation and other guidelines that may be updated after these Guidelines are published. Sponsors are recommended to check the information herein against any updated and current versions.

These Guidelines do not apply to medicines with therapeutic activity attributed to distinct ingredients that are inactivated, non-viable microorganisms and/or their components (known as postbiotics or paraprobiotics). If a postbiotic is a distinct active ingredient *within* a probiotic medicine, then these Guidelines apply to the probiotic ingredients. A medicine containing both probiotic and postbiotic ingredients is a synbiotic medicine.

These Guidelines do not apply to probiotic foods[1] such as fermented dairy products, fermented teas and fermented vegetables.

2.1 Guideline structure

These Guidelines are divided into three main sections:

Section 3, Quality control: outlines why it is important to control the quality parameters of probiotic medicines;

Section 4, Demonstrating compliance with legislative requirements: explains how to comply with the requirements outlined in Section 5;

Section 5, Applicable legislation: details the legislation that sponsors must comply with to control the quality of their probiotic medicine.

[1] Medicines and foods are regulated differently. The Food–Medicine Interface Guidance Tool can help to determine whether a probiotic product is a food or a medicine.

2.2 Glossary and abbreviations

- Australian Approved Name (AAN)
- Approved Biological Name (ABN)
- Australian register of therapeutic goods (ARTG)
- British Pharmacopeia (BP)
- Certificate of analysis (C of A)
- colony forming units (CFU)
- European Pharmacopoeia (Ph. Eur.)
- Good Manufacturing Practice (GMP)
- International council for harmonisation of technical requirements for pharmaceuticals for human use (ICH)
- pharmaceutical inspection convention and pharmaceutical inspection co-operation scheme (PIC/S)
- postbiotics (medicines with therapeutic activity attributed to distinct ingredients that are inactivated, non-viable microorganisms and/or their components. Also known as paraprobiotics)
- probiotic (live microorganisms that when administered in adequate amounts, are proposed to confer a health benefit on the host)
- quantified by input (QBI)
- species-level taxonomy in these Guidelines refers to naming of the *Genus* and *species* together
- strain-level taxonomy in these Guidelines refers to naming the *Genus, species and* strain together
- Therapeutic Goods (Manufacturing Principles) Determination 2020 (the Manufacturing Determination)
- Therapeutic Goods (Permissible Ingredients) Determination (the Permissible Ingredients Determination)
- Therapeutic Goods (Standard for Tablets, Capsules and Pills) (TGO 101) Order 2019 (TGO 101)
- *Therapeutic Goods Act 1989* (the Act)
- Therapeutic Goods Order No. 92 - Standard for Labels of Non-prescription Medicines (TGO 92)
- Therapeutic Goods Regulations 1990 (the Regulations)
- United States Pharmacopeia–National Formulary (USP–NF).

3 Quality control

This section defines 'quality' and outlines *why* controlling quality parameters is important for the safety and efficacy of probiotic medicines and is thus important for the health and safety of Australians.

The control of quality parameters ensures that a listed medicine is consistently manufactured to result in a final product that meets the design specifications and is safe and efficacious throughout its shelf life.

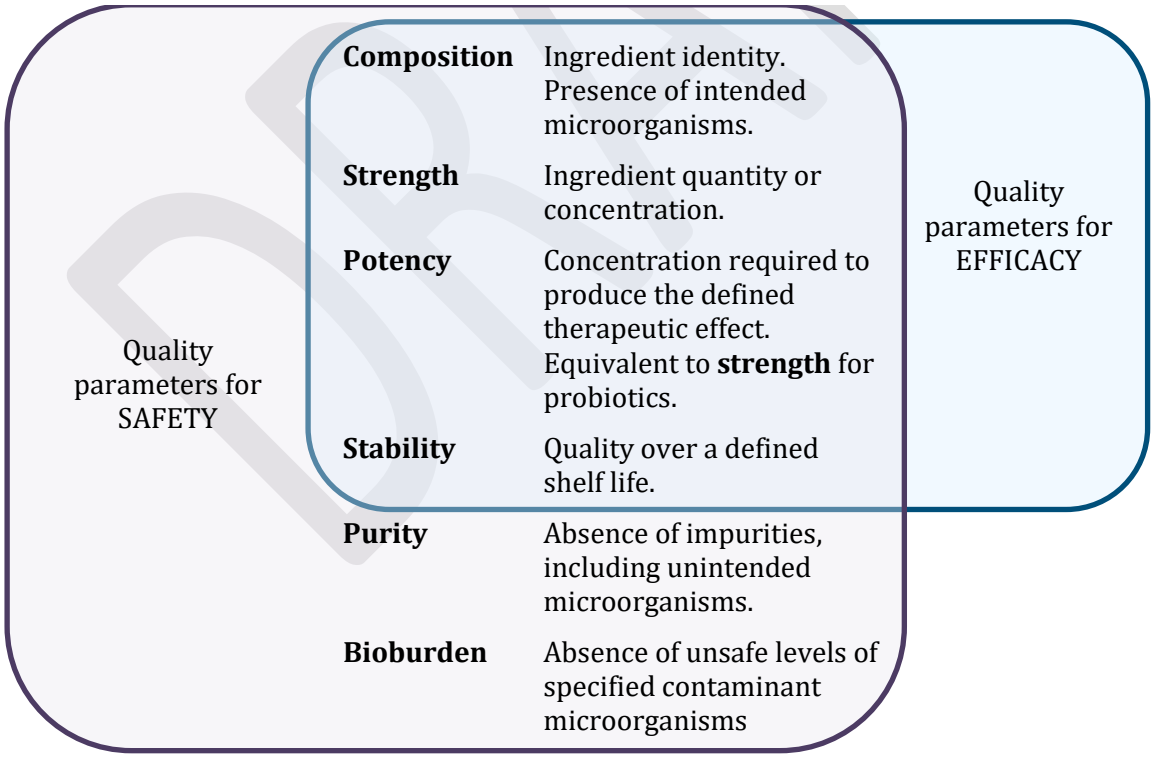
3.1 Quality parameters

Quality is defined in subsection 3(1) of the *Therapeutic Goods Act 1989* (the Act) as (bold added for emphasis):

> ***Quality,*** *in relation to therapeutic goods, includes the* ***composition***, ***strength***, ***potency***, ***stability***, *sterility,* ***purity, bioburden****, design, construction and performance characteristics of the goods.*

Figure 1 shows the quality parameters that relate to ensuring the safety and efficacy of probiotic medicines. There are legislative provisions in place that facilitate the control of these quality parameters, which is explained further in section **5** *Applicable legislation*.

Figure 1. Quality parameters for the safety and efficacy of listed probiotic medicines



3.2 Safety

A listed medicine must be safe for the purposes for which it is to be used, and the medicine must not harm any person (paragraphs 26A(2)(b) and 21A(5) of the Act, respectively).

The safety of listed medicines is in-part controlled by only permitting the use of ingredients in the Therapeutic Goods (Permissible Ingredients) Determination (under Schedule 4, items 3 and 8 of the Therapeutic Goods Regulations 1990). Controlling the quality parameters (see Figure 1) of a probiotic medicine ensures that the probiotic medicine continues to be eligible for listing (i.e. contains an ingredient specified in the Permissible Ingredients Determination) and suitable for supply as a low-risk medicine without TGA pre-market evaluation.

3.2.1 Bioburden

The definition of quality in subsection 3(1) of the Act includes **bioburden**, which is defined in the same subsection as:

> *the quantity and characteristics of microorganisms present in the goods or to which the goods may be exposed in a manufacturing environment.*

In the context of probiotic medicines, bioburden refers to the enumeration of contaminant microorganisms.

Sponsors must be able to demonstrate they have adequate control of bioburden in order for their medicine to be safe, and thus for it to remain on the ARTG. Sponsors are required to certify that the medicine is safe and complies with prescribed safety criteria (paragraphs 26A(2)(b) and 26A(2)(f) of the Act).

3.3 Efficacy

Efficacy is the capacity for therapeutic effect. The efficacy of a probiotic medicine depends on the presence of one or more specific therapeutically active ingredients in sufficient quantities over the shelf life of the medicine. As such, controlling the quality parameters in Figure 1 is critical for ensuring efficacy.

The ingredient in a probiotic medicine that is responsible for efficacy and stated in the information or evidence held by the sponsor (e.g. a clinical trial), is usually identified at the **strain** level; although, efficacy could potentially be attributed to a species or higher taxon. If a probiotic medicine's efficacy is not strain specific (i.e. species specific), then *any* strain in that species could confer the same therapeutic effect, and thus *any* strain in that species could be an ingredient responsible for efficacy in the medicine. Similarly, if the medicine's efficacy is genus specific, then *any* species (and strain within those species) could confer the same therapeutic effect and thus any species (and strain) in that genus could be an ingredient responsible for efficacy in the medicine.

For more information about efficacy, indications and evidence, refer to the Evidence Guidelines - How to demonstrate the efficacy of listed medicines is acceptable, Therapeutic Goods (Permissible Indications) Determination and the Guidance materials for permitted indications for listed medicines.

How the quality parameters can be controlled is dependent on whether the efficacy of a probiotic medicine is genus, species or strain specific. This is further explained below, in section **4** *Demonstrating compliance with legislative requirements*.

3.4 Stability

The stability of a medicine refers to a product that is shown to remain, or is likely to remain, within its design specifications (i.e. quality parameters in the product specification) throughout the shelf life when stored under the labelled storage conditions.

The quantities (and proportion) of active ingredients in probiotic medicines have the potential to vary from input at the start of manufacturing, to the final product at batch release, to the end of the medicine's shelf life. This variability arises because the active ingredients in probiotic medicines are live microorganisms whose rates and extents of growth, and hence their viable quantities, are responsive to multiple factors. These factors include product formulation (available growth factors such as microbial metabolites, excipients, residual water and oxygen), manufacturing processes (stresses such as cryopreservation, lyophilisation and grinding), type of container closure, and storage temperature.

Variability in quantity and proportion also arises between different strains which can differ in their viability and growth due to their different genotypes and phenotypes. For example, different strains may have different capacities to maintain their viability in response to refrigeration, low oxygen availability and low residual moisture.

As such, controlling the stability of a probiotic medicine is important for **efficacy** because throughout the shelf life of a probiotic, the quantity of an active microbial ingredient should remain no less than the claimed quantity on the label which provides the dose necessary for efficacy.

Controlling the stability of a probiotic medicine is also important for **safety** because throughout the shelf life of a probiotic, unsafe levels of specified contaminant microorganisms (bioburden) may occur.

4 Demonstrating compliance with legislative requirements

This section provides a practical summary of how sponsors can demonstrate compliance with applicable legislative requirements. The legislative requirements are explained in detail in section **5** *Applicable legislation*.

Sponsors may demonstrate compliance using approaches that are different to those outlined in this section. However, sponsors will be expected to document justifications for how their alternative approaches achieve the legislated outcomes outlined in section **5** *Applicable legislation*. An **evidence-based justification of quality** includes supportive high-quality scientific data (observations and measurements) that can be additionally strengthened by reasons or robust explanations using scientific concepts or mechanisms.

This section also discusses the TGA guidelines and international scientific guidelines such as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), which suggest ways to demonstrate compliance with the legislation but are not intended to be restrictive and can enable innovation.

4.1 How to determine which quality standards to comply with

There may be multiple default and ministerial standards that can apply to a listed probiotic medicine. Table 1 assists sponsors to determine which **quality** standards apply to their **final product**. The rationale behind these tables is explained in section **5.6** *Default standards* and section **5.7.2** *TGO 101 – Dosage forms that are tablets, capsules and pills*.

A specific monograph, a term used in Ph. Eur. (also called an individual monograph in the USP–NF), may apply to a medicine or an ingredient even where the title of the monograph and the name of the medicine or ingredient are not identical. Hereafter, this type of a monograph will be referred to as an '**individual monograph**'.

Where the name of a medicine or ingredient is a variant of the name of a monograph, the provisions of the monograph, including definitions, and the General Notices section of the relevant pharmacopoeia should be reviewed to determine whether the monograph applies. For more details on how to determine whether an individual monograph applies, refer to section **5.6.1** *Compliance with at least one default standard* and **5.7.2** *TGO 101 – Dosage forms that are tablets, capsules and pills*.

Table 1. Decision tool to determine which quality standards apply to a final product

For tablets or capsules, choose option 1 OR 2			
Option 1 - Ph. Eur./BP	Is there an individual monograph in the Ph. Eur./BP for the product? *	✗ If NO, comply with Division 3 of TGO 101 and Ph. Eur./BP 3053	
		✓ If YES, comply with the individual monograph and Ph. Eur./BP 3053 and Division 2 of TGO 101, OR Division 3 of TGO 101 and Ph. Eur./BP 3053	
Option 2 - USP–NF	Is there an individual monograph in the USP–NF for the final product or an ingredient in the final product? **	✗ If NO, comply with Division 3 of TGO 101 and Ph. Eur./BP 3053	
		✓ If YES, does it refer to USP–NF 64?	✗ If NO, comply with the individual monograph and Division 2 of TGO 101, OR Division 3 of TGO 101 and requirements relevant to the tablet or capsule in a USP–NF general chapter, but not USP–NF 64
			✓ If YES, comply with the individual monograph and Division 2 of TGO 101, OR Division 3 of TGO 101 and USP–NF 64
For dosage forms that are not tablets or capsules, choose option 1 OR 2			
Option 1 - Ph. Eur./BP	Is there an individual monograph for the final product in the Ph. Eur./BP? *	✗ If NO, comply with Ph. Eur./BP 3053	
		✓ If YES, comply with the individual monograph and Ph. Eur./BP 3053	
Option 2 - USP–NF	Is there an individual monograph in the USP–NF for the final product or an ingredient in the final product? **	✗ If NO, comply with Ph. Eur. /BP 3053	
		✓ If YES, is the probiotic labelled as conforming to USP–NF?	✗ If NO, comply with Ph. Eur./BP 3053
			✓ If YES, does the individual monograph refer to USP–NF 64?
			✗ If NO, comply with the individual monograph
			✓ If YES, comply with the individual monograph and USP–NF 64

* At the time these Guidelines were prepared there were no individual monographs in the Ph. Eur./BP for single or multi-strain products

** At the time these Guidelines were prepared there were no individual monographs in the USP–NF for single or multi-strain products. There are only single strain ingredient individual monographs.

4.2 Taxonomic level for identification, quantification and labelling

4.2.1 Microbial taxonomy

Microorganisms are named (taxonomically classified) by their genus, species (and sometimes subspecies) and strain. These classifications enable microorganisms to be identified as being different or similar to one another. The active microbial ingredients in a probiotic medicine have their identity, quantity and labelling at the taxonomic level of either strain (*Genus species* strain) or species (*Genus species*).

In these Guidelines:

- **Strain**-level taxonomy refers to naming that specifies the '*Genus species* strain' e.g. *Lactobacillus acidophilus* La-14
- **Species**-level taxonomy refers to naming that specifies the '*Genus species' e.g. Lactobacillus acidophilus*

A **strain** is a population of microorganisms that descends from a single organism or pure culture isolate. Different strains of a single species differ in their sets of genes (genotype) and their observed characteristics (phenotype). The phenotype of a strain results from interactions between its genotype and the environment, which affects its biochemistry, physiology, developmental processes and behaviour.

Consequently, identification of active microbial ingredients in probiotics **at the strain level** ensures they are distinct from other microbial ingredients with potentially different characteristics, risks and therapeutic effects (indications). Generally, strain-level identification is important for all probiotics, whether they are single-strain or multi-strain.

Many of the probiotic medicines that are currently listed on the ARTG contain several strains from at least one genus or species (see **Table 2**). These are called multi-strain probiotics.

Table 2. Example formulation of a multi-strain probiotic medicine

Genus	Species	Subspecies	Strain
Lactobacillus	*delbrueckii*	*Bulgaricus*	(Lb-87)
	acidophilus		(La-14)
Bifidobacterium	*breve*		(Bb-03)
	lactis		(Bi-07)
			(Bl-04)

4.2.2 Summary of taxonomic level for identification, quantification and labelling

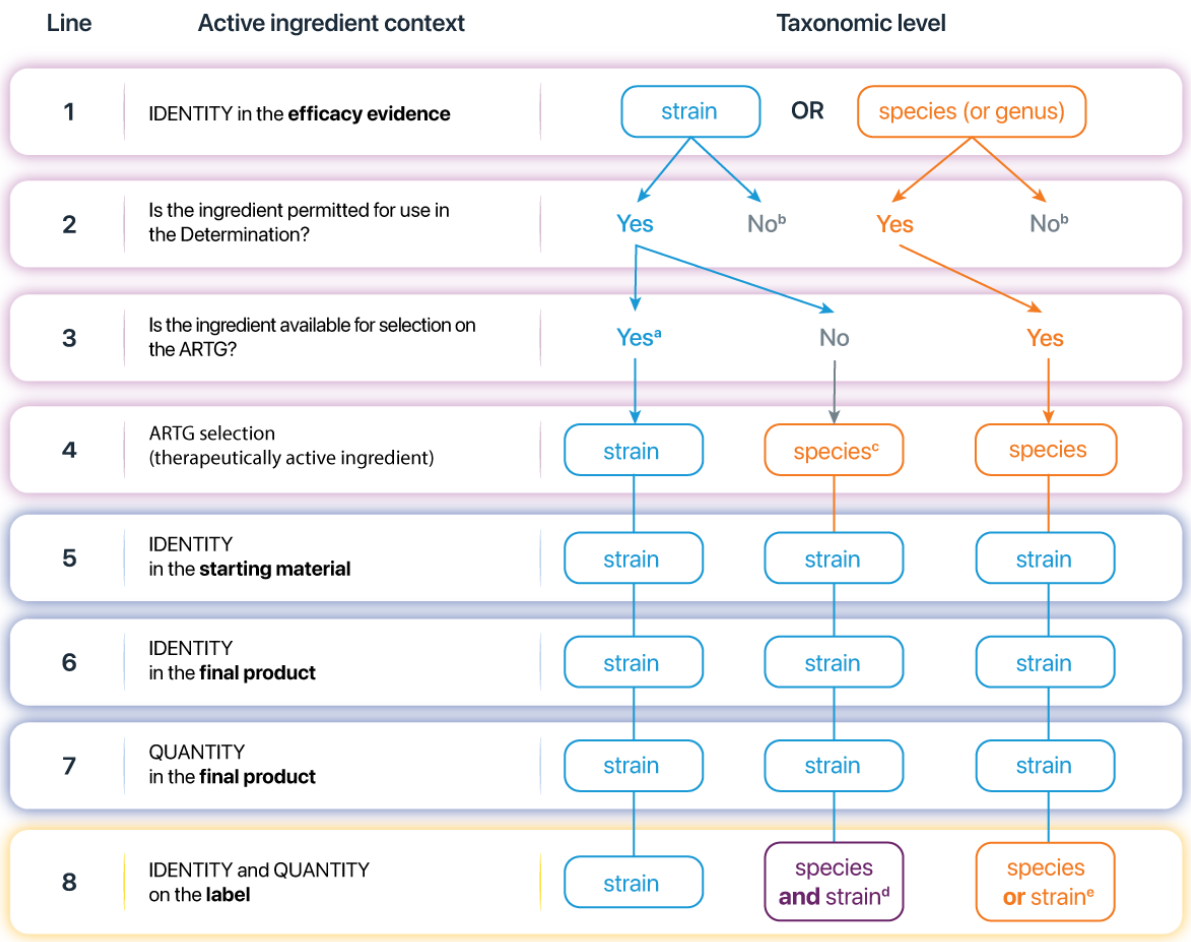
Figure 2 below summarises the taxonomic level at which an active microbial ingredient should be identified, quantified and labelled.

The taxonomic level for the active ingredient will depend on the:

- taxon responsible for efficacy in the evidence held by the sponsor
- taxon available in the Permissible Ingredients Determination
- taxon selected from the ARTG
- quality standards that apply to the product (see **Table 1**)
- quality standards that apply to the starting material (see **Table 4**).

Table 3 provides the applicable legislation and relevant explanatory sections in these Guidelines for each line in **Figure 2**.

Figure 2. Taxonomic level of the active ingredient



[a] At the time these Guidelines were prepared, there were no strains available for selection on the ARTG for listed medicines.

[b] Apply for the new substance to be included in the Permissible Ingredients Determination. Refer to section **5.5** *Permissible Ingredients Determination*.

[c] If the strain is permitted for use under the species in the Permissible Ingredients Determination, then select the corresponding species on the ARTG.

[d] When the **species** (*Genus species*) is selected on the ARTG, both the **species** (*Genus species*) **and strain** (*Genus species* strain) should be presented on the label if the relevant monograph is Ph. Eur. 3053; or if there is a relevant USP–NF monograph that states the labelling is to be at the strain level. Refer to **Table 1**, **Table 10**, **Table 11** and section **4.7** *Labelling*.

[e] Identity and quantity on the label should be at strain level (*Genus species* strain) if the relevant monograph is Ph. Eur. 3053. **Or** if there is a relevant USP–NF monograph that states an option for labelling to be at the species level (*Genus species*), identity and quantity on the label can be at species level. Refer to **Table 1, Table 10**, **Table 11** and section **4.7** *Labelling*.

Table 3. Explanatory sections in these Guidelines for each line in Figure 2

Line	Guideline section
1	**3.3** *Efficacy* **5.2** *Listing certification* **5.3** *Conditions of listing* **5.5** *Permissible ingredients Determination*
2	
3	**5.5** *Permissible ingredients Determination*
4	**5.5** *Permissible ingredients Determination*
5	**4.3** *Quality of starting materials* **5.6.2** *Ph. Eur. and BP* for information about characterisation of starting materials. ***5.6.3*** *USP–NF* for information about official substances, including starting materials. **5.8.3** *GMP – starting materials* for information about identification of starting materials during manufacturing.
6	**4.4** *Active ingredient identification in the final product* **4.5** *Active ingredient quantification in the final product* **5.1–5.5** for information about the Act and how it legislates the control of quality (e.g. identity and quantity). **5.6.2** *Ph. Eur. and BP* and **Table 10** for information about identification and quantification in the final lot. **5.6.3** *USP–NF* and **Table 11** for information about identification and quantification in the final lot when there is an applicable USP–NF monograph (e.g. single strain products) **5.7.2** *TGO 101 – Dosage forms that are tablets, capsules and pills* for information about the stated content of an active microbial ingredient.
7	
8	**4.1** *How to determine which quality standards to comply with* **4.7** *Labelling* **5.6.2** *Ph. Eur. and BP* and **Table 10** for information about identification and quantification on the label. **5.6.3** *USP–NF* and **Table 11** for information about identification and quantification on the label when there is an applicable USP–NF monograph (e.g. single strain products). **5.7.1** *TGO 92 – Labelling*

4.3 Quality of starting materials

Table 4 assists sponsors to determine which quality standards to comply with for their starting materials. Where there are no quality standards, sponsors are expected to develop the parameters and acceptance criteria to ensure the quality of their starting materials. For more

details on how to determine whether an individual monograph applies, refer to section **5.6.1** *Compliance with at least one default standard*.

Table 4. Decision tool to determine which quality standards apply to ingredients within a probiotic medicine

<table>
<tr><th colspan="4">For starting materials choose option 1 OR 2</th></tr>
<tr><td rowspan="3">Option 1 - Ph. Eur./ BP</td><td rowspan="3">Is there an individual monograph for the ingredient in the Ph. Eur./BP?</td><td rowspan="2">✗ If NO, is there an individual monograph for the ingredient in the USP–NF?</td><td>✗ If NO, develop scientifically justifiable quality parameters and acceptance criteria for the ingredient and use analytical method(s) that have been validated for their purpose</td></tr>
<tr><td>✓ If YES, comply with the individual USP–NF monograph</td></tr>
<tr><td colspan="2">✓ If YES, comply with the individual monograph</td></tr>
<tr><td rowspan="3">Option 2 - USP–NF</td><td rowspan="3">Is there an individual monograph for the ingredient in the USP–NF?</td><td rowspan="2">✗ If NO, is there an individual monograph for the ingredient in the Ph. Eur./BP?</td><td>✗ If NO, develop scientifically justifiable quality parameters and acceptance criteria for the ingredient and use analytical method(s) that have been validated for their purpose</td></tr>
<tr><td>✓ If YES, comply with the individual Ph. Eur./BP monograph</td></tr>
<tr><td colspan="2">✓ If YES, comply with the individual monograph</td></tr>
</table>

The requirements for starting materials, including testing of quality parameters, are explained in the following three guidelines. If a sponsor omits any of the steps outlined in these guidelines, then alternative measures to achieve the same level of quality assurance is necessary in downstream processes. For example, it may be possible for a sponsor/manufacturer to scientifically justify a reduction in testing of particular aspects of the starting material where extensive test history is established and instead may be able to justify conducting those tests on the final product.

Sampling and testing for listed and complementary medicines – Technical guidance on the interpretation of the PIC/S guide to GMP

- For starting materials and intermediate products, there are different sampling requirements depending on whether the **supplier has been approved, and the individual material has been qualified** or not.
- Until a **supplier has been approved, and the starting material is qualified**, each delivery of starting material should be approved by the Quality Unit only after full sampling and testing has been successfully undertaken.
- Once a starting material has been qualified, reduced sampling and testing can be performed; as outlined in the Sampling and Testing Guidance referenced above. A manufacturer must **perform critical tests on each delivery** and is permitted to rotate through all non-critical tests. It is not permissible to skip any test without adequate justification. Critical tests and non-critical tests must be defined and a suitable sampling plan adopted.
- **Identification** is considered a critical test for all starting materials. **Quantification**, with appropriate acceptance limits, is also considered a critical test where a label claim is made for the active ingredient. Other tests may also be critical, depending on the material and its functionality in the product, particularly where the material attributes are critical to ensuring product quality and/or stability. For example, a starting material should be tested to ensure that the ingredient complies with specific requirements in the Permissible

Ingredients Determination, or where moisture (water content or water activity) is a parameter that is critical to the stability of the probiotic good.

- For **intermediate and bulk products**, verify that each delivery is from an approved manufacturer with a current TGA licence or GMP clearance (PIC/S Guide to GMP, Part 1, Chapter 1). This usually involves receipt of the manufacturer's Certificate of Analysis (C of A). Conduct sufficient testing to ensure quality of the product, particularly where product quality may have been impacted during transport.

Starting material analytical procedure validation for complementary medicines

- Test procedures for starting materials, including quantification and identification of the active substance, must use analytical methods that are validated for that purpose.
- If the analytical procedure for starting material testing is included in the current edition of the Ph. Eur./BP /USP–NF, then validation of that procedure is not required. However, method transfer should be undertaken to ensure the test method is applicable at the point of use and appropriate for its intended purpose.

Supplier assessment, approval and qualification for listed and complementary medicines – Technical guidance on the interpretation of the PIC/S Guide to GMP

- A formal GMP or technical agreement for suppliers and manufacturers of raw materials is not required provided there are approved specifications, a C of A from the manufacturing site and a system of **supplier approval**.
- All suppliers should be approved before materials and products are used. Approval allows an assessment to be made of the suitability of the supplier to provide the starting and/or packaging material to the manufacturer of a medicinal product.
- Until **material** received from an approved supplier **is qualified**, each delivery of starting material should be approved by the Quality Unit only after full sampling and testing has been successfully undertaken.
- Reduced sampling and testing of starting materials may be performed once the supplier has been qualified and other conditions are met.

4.4 Active ingredient identification in the final product

Sponsors should demonstrate that the active ingredients required for efficacy (i.e. ingredients identified on the label) are in the **final product.** Refer to sections **5.6** *Default standards* and **5.8** *Good Manufacturing* Practice in these Guidelines, for legislation applicable to identification testing and quality control.

Sponsors should identify the active ingredients in the final product at strain level, which is generally irrespective of whether the taxon responsible for efficacy is at the genus, species or strain level. However, sponsors should check the current default standard (Ph. Eur./BP or USP–NF) that is relevant to their product and their efficacy evidence to assess whether they may identify at species or genus level instead of strain level. Refer to **Figure 2**, **Table 9**, **Table 10** and section **5.6** *Default standards*.

The TGA guideline PE009, the PIC/S guide to GMP for medicinal products – TGA interpretation and expectations for demonstrating compliance explains that a discriminatory **identification test** must be used to correctly identify the strain or strains of organisms claimed on the product label. Biochemical identification methods may not be reliable for this purpose and genotypic

identification methods should be employed, for example, 16S rRNA sequencing or PCR. Where a sponsor chooses to use an alternative analytical test or procedure to those presented in the relevant default standards, it must be appropriately validated to demonstrate that it is suitable for its intended purpose (see section **5.6.4** *Alternative tests for identification and quantification*).

Alternatively, where scientifically justified, it may be possible for a sponsor to control the identity of the active ingredients in the final product through appropriate controls of the starting material, such as those outlined in section **4.3** *Quality of starting materials*. However, it is the sponsor's responsibility to scientifically justify and ensure that the identity of the active ingredients remain unaffected by downstream processes and meets product specifications and label claims.

4.5 Active ingredient quantification in the final product

Sponsors should demonstrate that the active ingredients required for efficacy are in the **final product** at the correct amounts (i.e. as quantified on the label).

The simplest strategy is to conduct strain-level quantification as part of batch release testing (refer to **Table 9** in section **5.6.2** *Ph. Eur. and BP* and **Table 10** in section **5.6.3** *USP–NF*). The quantification test method chosen depends on the blend of ingredients in the medicine, as strains can be quantified by testing at the level of strain, species or genus (**Table 5**).

For example, a test at genus level (e.g. plate count method) could provide strain quantification data if there is only one strain per genus in a probiotic with multiple active ingredients (**Table 5**, scenario 2) or if the probiotic only contains one active microbial ingredient that is a single strain (scenario 1). However, if a medicine contains more than one strain per species then a strain-specific method to measure either CFU or viable cells is required (scenario 3).

Strains cannot be quantified at the level of genus or species in scenario 3, or genus in scenario 2 as the test result cannot distinguish the quantities of the different strains. Furthermore, such test results cannot detect any change in the ratios of the strains in the final product at batch release or at the end of the medicine's shelf life.

An alternative strategy available to sponsors is 'quantified by input' (refer to section **4.5.3**), provided that the data and information to scientifically justify this approach is held by the sponsor and manufacturer and is capable of demonstrating the quantity of each strain in the final product.

Sponsors should choose a strategy most appropriate for their circumstances. For example, if access to validated strain quantification methods is not available, then whichever alternative strategy is selected, sponsors must still be able to demonstrate that the correct amounts of active ingredients are in the final product.

Table 5. Examples of the taxonomic level of quantification testing depending on the microbial ingredients in the formulation

Scenario	Example product characteristics				Compliance expectations	
	Probiotic ingredients	✓ Taxa are different in the probiotic blend. ✗ Taxa are similar in the probiotic blend.			Taxonomic level of testing that would be sufficient to quantify the ingredients	Rationale
		Strain	Species	Genus		
1	*Bifidobacterium breve* (Bb-03)	✓	✓	✓	Genus	The only active microbial ingredient is a single strain
2	*Bifidobacterium breve* (Bb-03) *Lactobacillus acidophilus* (La-14)	✓	✓	✓	Genus	Each strain is from a different species and a different genus
3	*Bifidobacterium breve* (Bb-03) *Bifidobacterium lactis* (Bi-07)	✓	✓	✗	Species	Each strain is from a different species but the same genus
4	*Bifidobacterium lactis* (Bi-07) *Bifidobacterium lactis* (Bl-04)	✓	✗	✗	Strain	Each strain is from the same species and the same genus

4.5.1 Selecting and validating quantification methods

Analytical procedures (i.e. test methods) for quantifying the active ingredients in a medicine must be validated (refer to section **5.8.2** *GMP – Testing for quality*). The selected procedures should depend on whether their medicine has either one strain or multiple strains per genus or per species (see **Table 5** above for examples). Useful information can be found in the TGA guideline Finished product (medicine) analytical procedure validations for complementary medicines and the ICH guideline 'Q2(R1) Validation of analytical procedures: Text and methodology'. ICH Q2(R1) refers to characteristics for consideration during validation to ensure the analytical procedures are suitable for their intended purpose and provides a collection of terms and their definitions.

Various methods are capable of quantifying viable multi-strain probiotics to strain level, including quantitative real-time polymerase chain reaction (qPCR) and digital droplet PCR (ddPCR) with strain-specific PCR primers, flow cytometry with polyclonal antibody assays,

impedence flow cell cytometry, and whole genome sequencing with cross-referencing to strain genomes. Various staining techniques can be validated for excluding the number of non-viable cells from a viable cell count. Routine use of these methods in a Quality Control laboratory for a new specific intended purpose (such as for a particular product) may require method development before validation.

Culture methods are useful for quantifying microorganisms **at the level of genus**, but it is generally difficult or impossible to distinguish microorganisms at the strain level using these methods. Although, some species within the same genus can be differentiated using selective and differential culture media under different incubation conditions; the method should be validated for such a purpose. Culture methods are also limited as they cannot detect viable but non-culturable cells. Nevertheless, if this is the method selected, sponsors should still be able to demonstrate that each active ingredient is in the final product at the correct amount to support efficacy.

Where a sponsor chooses to use an alternative analytical test or procedure to those presented in the relevant default standards, the test must be appropriately validated to demonstrate that it is suitable for its intended purpose (see section **5.6.4** *Alternative tests for identification and quantification*).

4.5.2 Assay limit for content

Sponsors and manufacturers should consider the statistical variability in their quantification data during manufacture and method validation so that the **quantity of the active ingredient(s) in the final product is no less than the stated content throughout the shelf life of the product**.

The stated content is the quantity stated on the label and claimed to be present in each **tablet, capsule or other dosage form**, and is the same as the quantity documented in the **final product specification**. For example, '*Lactobacillus acidophilus*, No less than 2 billion CFU/capsule'.

GMP requires specifications for final products to include or provide reference to the quantitative requirements (i.e. the expected final yield) with the **acceptance limits** (PIC/S Guide to GMP for Medicinal Products - Part I, Chapter 4).

For dosage forms that are tablets or capsules (and when following the Australian specific requirements in Division 3 of TGO 101), ensure that the assay limit for the content of each active microbial ingredient in the final product is 'not less than stated content' (subsection 14(2) of Division 3 and item 4 of Schedule 2 of TGO 101). *Stated content* is defined in subsection 4(1) of TGO 101. Refer to section **5.7.2** *TGO 101 – Dosage forms that are tablets, capsules and pills* of these Guidelines.

For dosage forms that are *not* tablets or capsules, a relevant default standard applies instead of TGO 101. The statements in monographs from a relevant default standard (e.g. statements about an assay limit for content) are interpreted in accordance with the general notices from that default standard. The general notices of the Ph. Eur. and BP (Section 1.5.1.9) and the USP–NF (Section 4.10.20) require that a limit or acceptance criteria **includes or allows for analytical error and no further tolerances are to be applied to the limit**. This means that the quantity of each strain in the final product targets the quantity on the product specification and as labelled, but the measured quantity (on the certificate of analysis for each batch) must be no less than the lower assay limit stated in the product specification.

4.5.3 Quantified by input

Quantified by input (QBI) is a practice used to estimate the content of an active ingredient in a final product when it is not possible or practical to conduct an assay. QBI may be justified when a validated assay method for the ingredient in a final product is unavailable or is difficult to achieve because the medicine formulation is complex, or if an assay shows unresolvable matrix interference. Refer to the Australian regulatory guidance Quality for listed medicines for general QBI information.

It cannot be assumed that the quantities and ratios of individual strains in the final product are the same as the quantities and ratios at input as raw material. Nor can it be assumed that any particular strain will grow or survive in the same way as another strain or their species or genus (refer to section **3.4** *Stability*).

Therefore, if sponsors choose to use QBI, an **evidence-based justification** is required to demonstrate that the final product will contain the claimed amount ('no less than the stated content') of *each* viable active microbial ingredient strain (or species if applicable).

An **evidence-based justification** for QBI can include multiple sources, for example:

- Raw material supplier qualification and strain-level identification and quantification of raw microbial materials. Refer to section **4.3** *Quality of starting materials*.
- Process validation data (to demonstrate uniform composition of raw ingredients in product dosage units) to support the claim that the amount of added starting material is the same as the amount in the final product. For example, mixing validation studies using surrogate analytes to represent different probiotic strains could be performed to demonstrate that appropriate quantities of each ingredient are present in the in-process bulk substance. Also, fill validation studies using surrogate analytes to represent different probiotic strains could be performed to provide assurance that the appropriate quantity of each probiotic is present in each dosage form.
- **Water activity** data collected during product development, process validation, and/or routine testing of the final product to demonstrate how it is relevant to any change in the quantities of viable active microbial ingredients from input to the final product. If dormancy of strains at a particular water activity level is claimed, scientific data to substantiate this claim and its relevance to the specific strains in the medicine should be collected. For example, data to demonstrate that the quantity of viable cells for a strain or mixture of strains do not change by significant levels over time when the water activity is below a certain value. For the data to be relevant to the product, the water activity test should be conducted on a sample comparable to the product in relation to ingredient components, the type of container, and the storage temperature and humidity.

  If control of water activity forms part of the sponsor's strategy to ensure quantity of active ingredients in the final product, then Pharmacopoeial methods should be used. Pharmacopoeial methods include USP–NF <922> 'Water activity' (which includes an application for optimising the stability of probiotics); Ph. Eur./BP 3053 requires tests for either water (2.5.12), loss on drying (2.2.32) or water activity (2.9.39); and BP Appendix IX M 'Water-solid interactions: Determination of sorption-desorption isotherms and of water activity'.

4.6 Stability of the final product

Stability studies are used to assure that a medicine's specifications (such as active ingredient identity and quantity) will be maintained under the conditions described on the medicine label for the duration of its shelf life.

The TGA guideline on the PIC/S guide to GMP for medicinal products recommends basing on-going stability studies on the principles of ICH Q1 Stability. The ICH guideline ICH Q1A(R2) Stability testing of new drug substances and products refers to using analytical procedures that are fully validated and stability indicating. The TGA Technical guidance on the interpretation of the PIC/S Guide to GMP On-going stability testing for listed and complementary medicines describes ways that a manufacturer may operate to demonstrate compliance with the relevant manufacturing principles.

Stability data for active ingredients could be generated for individual strains, or combinations of strains, in conjunction with any other relevant information. This type of data should demonstrate that the stability of each strain is not significantly affected when the strains are combined in a product under the claimed storage conditions and throughout its shelf life.

Stability data from a factorial design study (such as to assess the effect of strain combinations on each strain) may be applicable (refer to ICH Q1D, bracketing and matrixing designs for stability testing of new drug substances and products). For example, test samples are created with *Lactobacillus acidophilus* (NCFM) and two other strains so that all samples contain all possible combinations of one, two or three strains. All samples are then tested under conditions relevant to the product(s), including but not limited to storage time, temperature, humidity, excipients and container type. Then, if the number of viable cells of *L. acidophilus* (NCFM) remains stable in all samples for the duration of the test, then this data could demonstrate that the stability of *L. acidophilus* (NCFM) is not significantly affected when in a product containing any of the two other strains and under similar conditions.

4.6.1 Accelerated stability studies

Accelerated stability studies are unlikely to substantiate the stability of a probiotic medicine. Microbial growth and decay respond to multiple factors, and data from earlier time points in a stability study (such as at 6 months) may not reflect any clear trend towards a later endpoint. Therefore, unless demonstrated or scientifically justified, the viability of microorganisms in an accelerated study of a final product stored at 25°C for 6 months, as an example, cannot be assumed to be the same as their viability in the final product stored at 2–8°C for 24 months.

Any extrapolation from an accelerated or a short-term study to the full-term shelf life of a probiotic medicine should be supported by scientific data to demonstrate that the mathematical model or equation used in the extrapolation is reliable and valid.

4.6.2 Grouping of on-going stability testing

A listed medicine may be *grouped* into an on-going stability program for a representative medicine instead of being placed on its own specific on-going stability program. Further information can be found in the TGA guideline On-going stability testing for listed and complementary medicines.

The grouping approach should be supported by scientific data demonstrating that the formulation (all ingredients), dosage form, method of manufacture and primary packaging material are comparable between the listed medicine and the representative medicine. Additionally, grouped probiotic medicines should also be supported by scientific data demonstrating that the stability of any different genera, species or strains in the medicine are comparable to the reference medicine on the stability program. Any differences in the rates of change of strain quantities over time between the historical data and real-time data should be evaluated scientifically to assess whether the data supports the stability of the product.

The active ingredients in probiotic medicines are live microorganisms whose rates and extents of growth, and hence their quantities and viability, are responsive to multiple factors (refer to

section **3.4** *Stability*). Therefore, adequate data about stability-indicating variables (e.g. viable quantities) of each active ingredient strain should be collected to demonstrate that grouping with a representative medicine is appropriate.

4.6.3 Overage

Overage is the quantity of an ingredient added at the start of manufacturing that is additional to the claimed quantity. The purpose of overage is for a product to maintain the claimed amount of viable active microbial ingredient despite expected decreases throughout manufacturing and the product's shelf life.

The overage for each active microbial ingredient should be considered during manufacture and during analytical method validation so that the quantity is no less than the stated content throughout the shelf life of a product (refer to section **5.7.2** *TGO 101 – Dosage forms that are tablets, capsules and pills*, and for dosage forms other than tablets, capsules or pills refer to section **4.5.2** *Assay limit for content*).

The amount of overage should also be considered when a sponsor certifies their product is of acceptable safety (paragraphs 26A(2)(b) and 26A(2)(f) of the Act).

4.7 Labelling

If an active microbial ingredient name is at the level of **species** ('*Genus species*') in the Australian Approved Name (AAN) list, the Permissible Ingredients Determination and ARTG entry, then the **species** name must be on the label to comply with TGO 92, paragraph 8(1)(b). Refer to the Approved Biological Names (ABNs) list, which is a category within the AAN list.

If Ph. Eur./BP 3053 is an applicable standard, then **in addition** to the species name, the **strain** name ('*Genus species* strain') must also be on the label (**Table 10**). Alternatively, if the applicable standard is a monograph in the USP–NF, then follow the recommendation for labelling in that monograph and in USP–NF 64 if cited in the individual monograph (**Table 11**).

Refer to **Figure 2** for a schematic showing when the name of an ingredient is required to be on the label at strain or species level or both.

Compliance with both TGO subclause 9(3) and the applicable default standard (either Ph. Eur./BP 3053 or USP–NF 64) can be achieved by presenting the strain name on the label in a manner that does not disrupt the cohesive unit. **Table 6** provides examples of label presentation of the ingredient and quantity depending on the taxonomic format of the AAN, in the Determination and in the ARTG entry.

Table 6. Label presentation of the AAN and quantity in a cohesive unit

Taxonomic format of the ingredient AAN, in the Determination and ARTG entry	Label presentation
Genus species (strain)	The AAN [*Genus species* (strain)] is followed by the quantity. For example: *Lactobacillus acidophilus* (NCFM) 25 billion CFU/capsule

Taxonomic format of the ingredient AAN, in the Determination and ARTG entry	Label presentation
Genus species	The AAN (*Genus species*) is followed by the quantity. For example: *Lactobacillus acidophilus* 50 billion CFU/capsule In addition, strain information is separately presented from the cohesive unit of the medicine name, AANs and quantities. For example: *L. acidophilus* strains: NCFM and La-14, each 25 billion CFU/capsule [or] *L. acidophilus* strains: NCFM 25 billion CFU/capsule, La-14 25 billion CFU/capsule [or when only one strain per species] *L. acidophilus* strain: La-5

AAN, Australian Approved Name; CFU, colony forming units

5 Applicable legislation

This section details the legislative framework and requirements that a sponsor *must* comply with to control the quality of their listed probiotic medicine. This section provides the legislative basis for the information in section **4** *Demonstrating compliance with legislative requirements*.

5.1 The Act

The Act (*Therapeutic Goods Act 1989*) provides a system of controls for the quality, safety and efficacy of therapeutic goods. To ensure the quality, safety and efficacy of their medicine, a sponsor must comply with the Act, and delegated (secondary) legislation under the Act, such as Regulations, Standards, Orders, Codes and Determinations.

There are legal consequences for sponsors who fail to control the quality, safety and efficacy of their medicine in accordance with legislative requirements. This may include cancellation and/or recall of the medicine, issuing of infringement notices or formal court action. If a medicine is cancelled from the ARTG, it is an offence under the Act to manufacture, supply for use, import or export the medicine (subject to limited exceptions).

Non-compliance with Chapter 3 of the Act (including Part 3-1 'Standards', Part 3-2 'Registration and listing of therapeutic goods', and Part 3-3 'Manufacturing of therapeutic goods') may incur civil penalties and criminal offences, unless stated otherwise (for example, where there is consent under sections 14/14A, or exemptions under sections 18 or section 34).

Refer to **Table 7** for a list of the more relevant legislation for regulating quality, and for links to delegated legislation, pharmacopeia, and TGA-adopted guidance.

Note that legislation other than that mentioned in these Guidelines may also be relevant to a sponsor's particular situation. For general guidance on other legislation, refer to the TGA guideline Overview of the regulation of listed medicines and registered complementary medicines.

Table 7. Legislative provisions relevant to quality

Section in these Guidelines	*Therapeutic Goods Act 1989* (section or subsection)		Delegated legislation, relevant pharmacopoeia or guidance
5.2	Listing of certain medicines – matters that applicant must certify	26A(2)	
5.3	Conditions of listing – must be complied with. Non-compliance may lead to cancellation	28	See, also, Therapeutic Goods (Listed Medicines—Conditions of Listing) Determination 2022
5.4	Cancellation of listing – various grounds	30(1), 30(1A), 30(2)	
5.5	Permissible ingredients – listed medicines must only contain permissible ingredients	26BB	Therapeutic Goods (Permissible Ingredients) Determination
5.2, 5.3	Permissible indications – medicines listed (under s 26A) can only use permissible indications	26BF	Therapeutic Goods (Permissible Indications) Determination
5.6	Definition of 'default standard' See, also, paragraphs (b), (c) and (d) of definition of 'standard'	3(1)	European Pharmacopeia (Ph. Eur.) British Pharmacopeia (BP) United States Pharmacopeia–National Formulary (USP–NF).
	Special provisions relating to ministerial standards and default standards – particularly where there are inconsistencies or questions of application	13	
	Criminal offences, or civil penalty provisions, for importing, supplying or exporting goods	14, 14A	

Section in these Guidelines	*Therapeutic Goods Act 1989* (section or subsection)		Delegated legislation, relevant pharmacopoeia or guidance
	that do not comply with standards		
5.7	Ministerial standards, orders	10 See also 13, 14, 14A	Therapeutic Goods Order No. 92 - Standard for Labels of Non-prescription Medicines (TGO 92) Therapeutic Goods (Standard for Tablets, Capsules and Pills) (TGO 101) Order 2019 (TGO 101)
5.8	Manufacturing principles – to be observed in manufacture of therapeutic goods	36	Therapeutic Goods (Manufacturing Principles) Determination 2020 Guide to Good Manufacturing Practice for Medicinal Products (PIC/S Guide to GMP)

5.2 Listing certification

When an application is made to list a medicine under section 26A, the applicant must certify all matters under subsection 26A(2) of the Act, including that the information included in or with the application is correct (26A(2)(k) of the Act). If required by the Secretary (under subsection 31(2) of the Act), the applicant must be able to provide information or documents relating to their certifications. As such, the applicant must be able to demonstrate that their certifications are true and accurate. Where certifications are incorrect this may lead to cancellation.

The certifications most relevant to controlling the quality, safety and efficacy of probiotic medicines are included in **Table 8**.

Table 8. Certifications most relevant to quality, safety and efficacy

Paragraph of the Act	Certification
26A(2)(b)	The medicine is safe for the purposes for which it is to be used.
26A(2)(ca) and (cb)	The medicine does not contain an ingredient that is not specified in a determination under paragraph 26BB(1)(a); and if a determination under paragraph 26BB(1)(b) specifies requirements in relation to ingredients being contained in the medicine—none of the requirements have been contravened. Note: This certification relates to compliance with the Permissible Ingredients Determination.

Paragraph of the Act	Certification
26A(2)(d)	The medicine conforms to every standard (if any) applicable to the medicine. Note: Standards include ministerial standards such as TGO 92 and TGO 101, and the default standards Ph. Eur., BP and USP–NF.
26A(2)(f)	The medicine complies with all prescribed quality or safety criteria applicable to the medicine.*
26A(2)(fc)	The applicant holds information or evidence showing the medicine's specifications will be maintained under the conditions set out on the medicine's label until the medicine's expiry date
26A(2)(fd) and (fe)	Each indication proposed to be accepted in relation to the inclusion of the medicine in the Register is covered by a determination under paragraph 26BF(1)(a); and if a determination under paragraph 26BF(1)(b) specifies requirements in relation to an indication proposed to be accepted in relation to the inclusion of the medicine in the Register—none of the requirements have been contravened. Note: This certification relates to compliance with the Permissible Indications Determination.
26A(2)(ja)	The applicant holds information or evidence to support each indication proposed to be accepted in relation to the inclusion of the medicine in the Register; and the information or evidence complies with any requirements specified in a determination under subsection (2B).
26A(2)(e), (h) and (i)	If the medicine has been manufactured in Australia—each step in the manufacture of the medicine has been carried out by a person who is the holder of a licence to carry out that step; and all the manufacturers of the medicine are nominated as manufacturers in the application; and the applicant has, with manufacturers of the medicine who are manufacturers of the prescribed kind, written agreements containing such matters as are prescribed.*
26A(2)(k)	The information included in or with the application is correct.

* At the time these Guidelines were prepared there was nothing prescribed in the *Therapeutic Goods Regulations 1990* for the purposes of paragraphs 26A(2)(f) or 26A(2)(i).

5.3 Conditions of listing

Some conditions apply automatically to listed medicines and are imposed by section 28 of the Act (through the Therapeutic Goods (Listed Medicines—Conditions of Listing) Determination 2022). Conditions of listing are also able to be imposed, as a matter of discretion, by a delegate under section 28.

Under subsection 28(6) of the Act, a sponsor must (at any time while their medicine remains listed) provide **information or evidence** to the Secretary, if asked to do so, that supports a claim in relation to their medicine (other than a claim that is an indication). This can include claims about the shelf life of the medicine. The information or evidence **must be held at the time of listing** and **retained at all times while the medicine remains listed**.

Another condition of listing is that under subsection 28(7) of the Act. The sponsor must (at any time while the medicine remains listed) provide **information or evidence** to the Secretary, if asked to do so, that supports an indication that is accepted in relation to the inclusion of the medicine in the Register. This information or evidence **must be held at all times while the medicine remains listed**. While this condition is typically associated with literature evidence (such as clinical trial articles), the information or evidence may also include quality-related data that demonstrates the manufactured product can provide the necessary active ingredients at the correct dose in alignment with the literature evidence used to support the efficacy of the medicine.

5.4 Cancellation of listing

Listed probiotic medicines that are found to be non-compliant under provisions controlling quality may be cancelled from the ARTG and can no longer be sold in Australia. Examples of cancellation provisions relevant to controlling quality are included in **Table 9**.

Table 9. Provisions for cancellation of listing most relevant to controlling quality

Paragraph of the Act	Cancellation provision
30(2)(a)	The Secretary may cancel the listing of the goods from the ARTG if it **appears** to them that the **quality, safety or efficacy of the goods is unacceptable**.
30(2)(ba)	The Secretary may cancel the listing of the goods from the ARTG if it appears to the Secretary that any of the **certifications** under paragraphs 26A(2)(b), (c), (d), (da), (f), (fa), (fb), (fc), (h), (i), (j), (ja) or (k) or subsection 26A(2A) **are incorrect**.
30(2)(c)	The Secretary may cancel the listing of the goods from the ARTG if the sponsor has refused or **failed to comply with a condition** to which the inclusion of the goods is subject (other than the condition under paragraph 28(5)(d)). Note: Refer to section **5.3** for information about more relevant conditions of listing.

5.5 Permissible Ingredients Determination

Listed medicines must only contain ingredients that are in the Therapeutic Goods (Permissible Ingredients) Determination (the Permissible Ingredients Determination) and they must not contravene any of the requirements for an ingredient.

When applying to list a probiotic medicine on the ARTG, each active microbial ingredient selected from the Permissible Ingredients Determination must be at the appropriate taxonomic level of **strain** or **species** relied upon for the claimed efficacy. Refer to **Figure 2** for information about when efficacy evidence is held for the strain, but only species are available for selection when listing a medicine on the ARTG.

Active microbial ingredients are specified in Column 2 of the Permissible Ingredients Determination. Column 3 may also include specific requirements permitting the use of certain **strains** for that species however these strains are not separate ingredients under the

Permissible Ingredients Determination (section 5 in the Determination refers). As such, those strains are not available as separate ingredients when listing a medicine on the ARTG.

If a strain (or species) is not in the Permissible Ingredients Determination, then an application for evaluation of a new substance can be submitted to the TGA. See Requirements for microorganism characterisation for Listed Medicines and Registered Complementary Medicines and Application requirements for new substances in listed medicines.

If an active microbial ingredient is permitted for use in the Permissible Ingredients Determination, there will be a corresponding Australian Biological Name (ABN) in the Ingredients Table in the TGA Business Services (TBS) portal for selection during a listing application. For more information about ABNs, see Approved names for biological ingredients (not cells and tissues).

5.6 Default standards

Therapeutic goods supplied in, exported from or imported into Australia **must comply with applicable standards** (Part 3-1 of the Act). Criminal offences and civil penalties apply to persons who do not comply and who otherwise do not have consent (sections 14/14A of the Act). For more information refer to the guidance Compliance with ministerial and default standards.

Ministerial standards are also known as a Therapeutic Goods Order (TGO) (refer to section **4.7** *Ministerial standards*).

A default standard refers to statements in monographs in the British Pharmacopoeia (BP), the European Pharmacopoeia (Ph. Eur.), and the United States Pharmacopeia–National Formulary (USP–NF) (except for statements or monographs exempted by the Minister), as interpreted in accordance with the General Notices section of the relevant pharmacopoeia.

When an application is made to list a medicine under 26A(1) of the Act, the applicant **must certify that the medicine conforms to every standard** (if any) applicable to the medicine (26A(2)(d) of the Act). Certifications must be correct. As noted above, the Secretary may cancel the listing of the medicine from the ARTG if it appears to the Secretary that the certification is incorrect (30(2)(ba) of the Act).

5.6.1 Compliance with at least one default standard

Section 13 of the Act relates to the application of ministerial standards and default standards in particular circumstances. In short, testing to control the quality of active microbial ingredients **must be in accordance with at least one** default standard to which a medicine is subject (subsection 13(7) of the Act). However, the harmonisation of relevant monographs in the Ph. Eur./BP context also facilitates this outcome (see further below).

A specific monograph, a term used in Ph. Eur. (also called an individual monograph in the USP–NF), may apply to a medicine or an ingredient even where the title of the monograph and the name of the medicine or ingredient are not identical. Where the name of a medicine or ingredient is a variant of the name of a monograph, the provisions of the monograph, including definitions, and the General Notices section of the relevant pharmacopoeia should be reviewed to determine whether the monograph applies. In addition, when a medicine is a **tablet or capsule**, it may be the subject of an 'applicable monograph'. For further guidance see section **5.7.2** *TGO 101 – Dosage forms that are tablets, capsules and pills* in these Guidelines.

For a probiotic medicine, the most relevant monograph from the default standards is **Ph. Eur./BP 3053**[2], which refers to the European and British Pharmacopoeias, general monograph 3053 'Live biotherapeutic products for human use' (Official in April 2019)

USP–NF 64, which refers to the United States Pharmacopeia National Formulary, general chapter 64 'Probiotic tests' (Official on 1 August 2019) applies to a probiotic medicine if it is labelled as conforming to the USP or NF (USP–NF 'General notices and requirements' section 3.10.20.) and if there is a USP–NF individual monograph that is relevant and refers to USP–NF 64. For example, the individual USP–NF monograph for *Lactobacillus acidophilus* (Strains La-14 or NCFM) refers to USP–NF 64.

This means that generally **Ph. Eur./BP 3053 must be complied with if a probiotic medicine has no relevant USP–NF individual monograph, OR if it does have a relevant USP–NF individual monograph but the medicine is not labelled as conforming to the USP or NF.**[3]

Each relevant default standard applies in its entirety. A medicine does not comply with an entire default standard if a requirement within cannot be performed or met. The general notices sections of Ph. Eur., BP and USP–NF express that *all* requirements in relevant individual monographs (and relevant applicable general monographs or general chapters) must be met to demonstrate compliance with the standard. Readers should refer to the relevant text in the pharmacopoeia in full.

5.6.2 Ph. Eur. and BP

Ph. Eur. and BP standards contain general monographs and individual monographs. A medicine may be subject to general and/or individual monographs—even when cross references to applicable general monographs are not given in individual monographs.

The following is a broad outline of requirements in the Ph. Eur./BP 3053 and the general notices sections in these pharmacopoeias. Readers should refer to the relevant parts of the pharmacopoeia in full.

[2] Texts from the Ph. Eur., BP and USP–NF pharmacopoeias may be 'harmonised' (developed into a global quality standard) with another pharmacopoeia, meaning they have the same technical requirements (unless stated otherwise in their text). For example, the general monographs Ph. Eur. 3053 and BP 3053 are harmonised and are thus expressed herein as Ph. Eur./BP 3053.

[3] In comparison, in the TGO 101 context, a USP–NF monograph for a dietary supplement can be an applicable monograph for the purposes of the TGO irrespective of whether the good is labelled as conforming to the USP or NF. Refer to section **5.7.2** *TGO 101 – Dosage forms that are tablets, capsules and pills* of these Guidelines.

Table 10. Outline of Ph. Eur./ BP 3053 requirements for identification and quantification

Pharmacopoeia Section heading	Identification	Quantification
Final lot	▪ To ensure manufacturing consistency and product quality, identification in the final lot should confirm that the yield is of the intended strain. ▪ Each microorganism in the final lot must be identified by a suitable method—at the level of strain. ▪ A suitable identification method may be used if it has been validated for the intended purpose and has thus demonstrated its ability to unequivocally identify the microorganism in the product at the level of strain.	▪ The number of living microorganisms in a medicine must be determined by a suitable microbial enumeration test. ▪ Specific tests are not mandated, although the pour-plate method and the surface spread method are given as examples. ▪ The quantity (potency) of each strain must be expressed in CFU/g, CFU/mL or CFU per metric unit or dose; or as the number of viable cells per mL based on a viable-cell assay. ▪ The quantity of each strain must not be less than the stated value or it must be within the stated range.
Labelling	The label must state the name of each strain.	The label must state the quantity of each strain (CFU/g, CFU/mL, CFU/unit or viable cells/mL).
Stability	The Ph. Eur. and BP 'General notices' section 1.1 requires a preparation to comply throughout its period of validity, meaning that the medicine must comply with the quantification requirements for the duration of the product's shelf life.	
Characterisation (of starting material)	▪ Characterisation of each microorganism is at the level of strain. ▪ Identification includes determination of the phenotype and genotype of the strain by using methods such as macroscopic and microscopic examination, biochemical tests, molecular genetic tests, sequencing or mass spectrometry. ▪ The strain used for master seed lots must be identified by historical records that include information on its origin, subsequent manipulation and tests used for characterisation.	

5.6.2.1 Alternative approach to compliance

A medicine is of Ph. Eur. quality and BP quality if it complies with all of the requirements stated in the monograph (Ph. Eur. 'General notices', section 1.1.2.2; and BP 'General notices', Part II). In brief, these provisions also explain that when a manufacturer is assessing compliance with Ph. Eur./BP, they are not obliged to perform all of the tests in a monograph before release. The manufacturer may assure themselves that a product is of **pharmacopoeial quality** by other means, such as by design together with control strategy and data derived, for example, from validation studies of the manufacturing process.

Note that such alternative means of assurance should be scientifically justified. Such as with data from process validation or a history of compliant testing that is complemented by no changes to process or formulation. Also note that for critical quality attributes, all necessary and relevant tests for quality control must be carried out before release (refer to section **5.8.2** *GMP – Testing for quality* in these Guidelines).

In using this alternative approach to compliance, the manufacturer would be assuring conformance with the intended *outcome* of the Ph. Eur./BP 3053 (for example, ensuring the identity and quantity of each strain in the final lot, and use of a suitable microbial enumeration test). Examples of ways in which probiotic sponsors/manufacturers can achieve this is further explained in section **4** *Demonstrating compliance with legislative requirements* of these Guidelines.

Ultimately the sponsor is responsible for complying with the requirements in the Ph. Eur./BP 3053 and being able to provide sufficient information or evidence (including details of manufacturing assurances) to demonstrate such compliance. Also note that alternative analytical methods other than those described in the Pharmacopoeia may be employed for routine and control purposes (refer to section **5.6.4** *Alternative tests for identification and quantification* in these Guidelines).

5.6.2.2 Microbial contamination

Ph. Eur./BP 3053 refers to tests and acceptance criteria for enumeration of microbial contaminants. Tests include those referred to in Chapter 2.6.36 'Microbiological examination of live biotherapeutic products: Tests for enumeration of microbial contaminants', and in Chapter 2.6.38 'Microbiological examination of live biotherapeutic products: Tests for specified microorganisms'. In addition, Chapter 5.1.6 'Alternative methods for control of microbiological quality' may be used for qualitative, quantitative and identification tests of contaminant microorganisms.

5.6.3 USP–NF

A broad outline of the requirements in the general chapter USP–NF 64 and the USP–NF 'General notices and requirements' is in **Table 11.** Readers should refer to the relevant parts of the pharmacopeia in full. This outline is also subject to the following:

- Only official articles (official substances e.g. dietary ingredients, or official products e.g. dietary supplements) for which there is a monograph can comply with USP–NF. For the USP–NF to apply to dietary supplements that are not tablets or capsules, the label must also state that it conforms to the USP–NF.
- At the time these Guidelines were prepared, **monographs exist for single strain substances** (such as a starting material ingredient or a product that contains a single strain) but not for multi-strain substances or products. Refer to the pharmacopoeia for updated information.
- If there is an applicable monograph (such as for a starting material), then strain-level identification must be in accordance with the requirements in the individual monograph, applicable general chapters and the 'General notices and requirements'.
- USP–NF 64 is only applicable to the identification and quantification of microbial ingredients when USP–NF 64 is cited for that purpose in the monograph for the substance or product.
- For USP–NF 64 to become applicable to a multi-strain product, an individual monograph would first need to be developed and it would need to cite USP–NF 64. As noted, for

dietary supplements that are not tablets or capsules, the label must also state that it conforms to the USP–NF for the USP–NF to apply.

- If an individual monograph procedure or acceptance criteria is different to that in USP–NF 64, then the product is exempt from complying with that portion of USP–NF 64.

Table 11. Outline of USP–NF 64 requirements for identification and quantification

Pharmacopoeia Section heading	Identification	Quantification
Final lot	▪ Probiotic microorganisms are typically identified at the strain level as their characteristics are usually strain specific. ▪ A general testing procedure is provided for the identification of *Lactobacillus* and *Bifidobacterium* strains by PCR with specific primers; however, this general procedure refers to using the specific testing procedure, primer set and acceptance criteria in the individual monograph.	▪ The enumeration method is selective for the genera *Lactobacillus* and *Bifidobacterium* (independent of the strain). It should be verified to work for its intended purpose for each particular strain or formulation. ▪ The enumeration method is not suitable for quantifying individual strains in multi-strain probiotics. ▪ Alternative validated microbiological procedures for quantification (including automated methods) may be used if their equivalence to the pharmacopoeial procedure has been demonstrated.
Labelling	▪ Strain-level identification is recommended on the label. ▪ In cases where the therapeutic activity is scientifically substantiated to be genus or species specific, the dosage form may be labelled with the genus and species names.	▪ On the label, a total formulated enumeration of all probiotic ingredients throughout the product shelf life should be included at a minimum in CFU/g or CFU/serving—if cited as such in an individual (multi-strain) monograph.

5.6.3.1 Microbial contamination

USP–NF 64 recommends tests and acceptance criteria for contaminant microorganisms, including <2021> 'Microbial enumeration tests' and <2022> 'Microbiological procedures for absence of specified microorganisms—nutritional and dietary supplements'. In addition, guidance on selection, evaluation and use of microbiological methods as alternatives to compendial methods is provided in <1223> 'Validation of alternative microbiological methods'.

5.6.4 Alternative tests for identification and quantification

An alternative analytical test or procedure to those presented in the relevant default standards must be appropriately **validated** to demonstrate that it is suitable for its intended purpose. The TGA guideline Finished product (medicine) analytical procedure validations for complementary medicines provides further information.

Ph. Eur./BP 3053 requires *suitable methods* to be used for identification and quantification at the level of strain. In brief, the 'General notices' of the Ph. Eur., at section 1.1.1.2, defines 'suitable' (if criteria for suitability are not described in the text) to be when suitability is demonstrated to the satisfaction of the competent authority (e.g. the TGA). An example would be any appropriately validated strain-level test.

Ph. Eur. 'General notices', at section 1.1.2.5, also outlines that alternative methods may be used for control purposes—providing the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used.

BP 'General notices', Part II (on 'Assays and tests'), also allows for analytical methods other than those described in the Pharmacopoeia to be employed for routine purposes.

BP 'Supplementary Chapter 1 H' (on 'Biological assays and tests') explains that the methods of biological assay described in the Pharmacopoeia have been found satisfactory but will not necessarily be the best methods for use in all circumstances. In most instances, they may be replaced by other methods if it can be shown that such methods are at least equally accurate and precise and provide a measurement of the same active principles.

USP–NF 64 does not provide alternative methods for identification. However, for quantification, USP–NF 64 provides for alternative microbiological procedures (including automated methods) if their equivalence to the pharmacopoeial procedure has been demonstrated. Refer to USP–NF <1223> 'Validation of alternative microbiological methods'.

5.6.5 Relationship with ministerial standards

If there is an inconsistency between an applicable default standard and an applicable ministerial standard (such as the Therapeutic Goods Orders referred to in sections **5.7.1** *TGO 92 – Labelling* and **5.7.2** *TGO 101 – Dosage forms that are tablets, capsules and pills*), then the inconsistent requirement in the default standard is to be disregarded, not the entire default standard (subsection 13(2) of the Act).

Strain names and quantities are to be stated on the label in accordance with Ph. Eur./BP 3053 and USP–NF 64. This must be done in a manner that does not contravene the requirements in TGO 92. (refer to sections **4.7** *Labelling* and **5.7.1** *TGO 92 – Labelling*).

5.7 Ministerial standards

5.7.1 TGO 92 – Labelling

The Therapeutic Goods Order No. 92 - Standard for Labels of Non-prescription Medicines (TGO 92) requires, amongst other details, that the names (and quantities or proportions) of all active ingredients in a medicine be included on the medicine's label (see section 8, especially paragraph 8(1)(b) and (c) and sections 9 and 10 of TGO 92).

The '*name of an active ingredient*' is defined, as relevant, in section 6 of TGO 92 to mean the name that is accepted for inclusion in the Australian Approved Names list that can be searched in the Ingredients Table on the TGA Business Services website. These ingredients are named according to international scientific naming conventions to ensure their identities are unique, unambiguous and thus distinguishable.

For further guidance see Medicine labels: Guidance on TGO 91 and 92.

5.7.2 TGO 101 – Dosage forms that are tablets, capsules and pills

The Therapeutic Goods (Standard for Tablets, Capsules and Pills) (TGO 101) Order 2019 applies to listed (and registered) medicines in dosage forms that are tablets, capsules or pills. The section below focusses on the requirements for tablets and capsules, not pills.

Consider whether other ministerial or default standards are applicable to different dosage forms (e.g. powders, oil drops [pearls], chewable tablets and gummies).

5.7.2.1 Applicable monographs

The requirements for **tablets** and **capsules** outlined in section 8 of TGO 101 depend upon whether or not there is an **applicable monograph**.

In brief, an *applicable monograph* is defined in subsection 4(1) of TGO 101 to mean a default standard for a preparation or product in the BP, Ph. Eur., or USP–NF, that comprises an individual monograph, one or more applicable general monographs, and one or more applicable general chapters, interpreted in accordance with the general notices of the relevant pharmacopoeia. This is so, whether or not the goods are labelled as conforming to that standard.

Therefore, an applicable monograph exists if there is an **individual monograph** in the Ph. Eur, BP or USP–NF to which the probiotic tablet or capsule is subject. An applicable monograph is comprised of an individual monograph *together with* any applicable general monographs or general chapters. The general notices assist with determining when a general monograph or general chapter is applicable.

Ph. Eur./BP 3053 and USP–NF 64 are not applicable monographs for the purposes of TGO 101 by themselves because they are not individual monographs, instead they are a general monograph and a general chapter, respectively. Although, as explained below, the requirements in Ph. Eur./BP 3053 will still be applicable to probiotic tablets and capsules; and the requirements in USP–NF 64 will be applicable where a probiotic tablet or capsule is subject to an individual USP–NF monograph that refers to USP–NF 64.

For further guidance see Guidance for TGO 101.

5.7.2.2 Ph. Eur. or BP individual monographs

The Ph. Eur. and BP do not include any individual monographs for probiotic ingredients (at the time these Guidelines were prepared); therefore, there are no applicable monographs in Ph. Eur. or BP for the purposes of TGO 101.

5.7.2.3 USP–NF monographs for dietary ingredients or dietary supplements

Monographs for dietary ingredients or dietary supplements in the USP–NF are considered to be **individual monographs**, and therefore can be applicable monographs relevant to probiotic tablets and capsules for the purposes of TGO 101 (together with any applicable general monographs or general chapters). Further, in the TGO 101 context, this is the case for relevant USP–NF dietary ingredient or dietary supplement monographs irrespective of whether the medicine is labelled as conforming to the USP–NF (as provided for in the definition of 'applicable monograph' in subsection 4(1)).

The USP–NF includes individual monographs for probiotic species and specific strains. For example, the individual USP–NF monograph for *Lactobacillus acidophilus* (for strains La-14 or NCFM) would be an applicable monograph where relevant.

However, individual monographs for a probiotic species and strain are only applicable to formulated products (or starting materials) that contain a single strain—unless explained otherwise in the 'Definition' section of the monograph. Apart from this exception, an applicable monograph for a multi-strain probiotic would require an individual monograph for the formulated product.

A **USP–NF general chapter** can also be relevant to a tablet or capsule if there is a relevant USP–NF individual monograph that refers to the general chapter (such as the reference to the general chapter USP–NF 64 in the individual monograph for *Lactobacillus acidophilus*). With the exception that a general chapter is not relevant if an individual monograph refers to it for information purposes only (Section 3.10 of the USP–NF General notices).

5.7.2.4 Requirements for tablets and capsules

Table 2 provides a decision tool that summarises the following and assists sponsors with determining which parts of TGO 101 and default standards to comply with.

If an applicable monograph exists (there can be more than one), subsection 8(1) of TGO 101 specifies that a sponsor can elect to comply with that applicable monograph, subject to the matters specified in Division 2 (of Part 2 of TGO 101). **Alternatively**, a sponsor can elect to comply with the Australian specific requirements in Division 3 (of Part 2 of TGO 101) and the requirements relevant to the tablet or capsule specified in one of the general monographs/chapters of the Ph. Eur., BP or USP–NF.

In the absence of an applicable monograph, subsection 8(2) of TGO 101 specifies that a medicine must comply with the Australian specific requirements in Division 3 (of Part 2 of TGO 101) and the requirements relevant to the tablet or capsule specified in one of the general monographs/chapters of the Ph. Eur., BP or USP–NF.

In either case, when Division 3 applies, it applies *together with* the requirements specified in one of the general monographs or general chapters that is relevant to the tablet or capsule (from either the Ph. Eur., BP or USP–NF).

5.7.2.5 Not less than the stated content

The **Australian specific requirements** in Division 3 (of Part 2 of TGO 101) provide, among other things, that the assay limit for an active probiotic ingredient in a probiotic tablet or capsule must be 'not less than the stated content' (subsection 14(2) and Schedule 2). The *stated content* means the quantity of the active ingredient that is stated on the label and is thus claimed to be present in each capsule (or tablet) (subsection 4(1) of TGO 101).

5.8 Good Manufacturing Practice

When an application is made to list a medicine under section 26A, the applicant must certify matters in relation to manufacturing under paragraphs 26A(2)(e), (h) and (i) of the Act (refer to section **5.2** *Listing certification* in these Guidelines).

Manufactured therapeutic goods, and the person manufacturing the therapeutic goods, must comply with Part 3-3 of the Act 'Manufacturing of therapeutic goods'. Good Manufacturing Practice (GMP) is a system that ensures the quality of a medicine is consistently and adequately controlled. The PIC/S Guide to GMP for Medicinal Products is legally enforced in Australia

through section 36 of the Act and the Therapeutic Goods (Manufacturing Principles) Determination 2020 (the Manufacturing Determination).

The PIC/S Guide to GMP includes controls for the quality of probiotic medicines such as ongoing stability (e.g. Chapter 6), starting materials (e.g. Chapter 1), supplier qualification (e.g. Chapter 5), product Quality Reviews (e.g. Chapter 1), and manufacturing validations and equipment qualification requirements (e.g. Annex 15).

Where the PIC/S Guide to GMP states that a procedure or requirement '*should*' be followed, the manufacture of therapeutic goods **must** follow the procedure or requirement in order to comply, subject to certain exceptions (Manufacturing Determination, Schedule 1, Part 1(2)).

The exceptions allow for a particular procedure or requirement not to be adopted, or an alternative to be adopted. However, the manufacturer must demonstrate that this will not increase the risk that the goods could (or could potentially) cause harm or injury, **will not increase the risk of the goods failing to comply with an applicable standard** or **relevant condition of listing**, and will not depart from any applicable record keeping requirements contained in the PIC/S Guide to GMP.

Voluntary procedures or requirements specified in an Annex to the PIC/S Guide to GMP do not need to be complied with (for example, Annex 20).

5.8.1 On-going stability

On-going stability testing of listed probiotic medicines must comply with the applicable procedures and requirements in Chapter 6 'Quality Control' of the PIC/S Guide to GMP for Medicinal Products - Part I. See the TGA guideline On-going stability testing for listed and complementary medicines for technical guidance.

An on-going stability program monitors a medicine over its shelf life to determine that it remains, and can be expected to remain, within its specifications under the labelled storage conditions (PIC/S Guide to GMP, Part 1, Chapter 6). The stability program for a medicine must be described in a written protocol, which must include (among other things) relevant test methods and acceptance criteria. This ensures that a probiotic medicine will deliver the required quantity of each active ingredient strain (or species if applicable) per dose throughout the shelf life (in accordance with a sponsor's certification under paragraph 26A(2)(fc) of the Act).

5.8.2 Testing for quality

Quality Control ensures that tests are carried out for all critical quality attributes and materials are not released for use, sale or supply until their quality is satisfactory. This requires validated test methods (PIC/S Guide to GMP, Part 1, Chapter 1), using approved testing methods for the product (Chapter 6), recording data with references to specifications and testing procedures (Chapters 4 and 6), and test method transfer (e.g. between laboratories) requirements (Chapter 6).

For guidance on test method validation see Finished product (medicine) analytical procedure validation for complementary medicines, Starting material analytical procedure validation for complementary medicines and in the ICH quality guidelines.

5.8.3 Starting materials

The starting materials for a probiotic medicine include all active microbial ingredient strains (and excipients) that are input at the start of manufacturing. Starting materials are regulated and quality controlled through a system of vendor qualifications, supply chain traceability,

approved specifications and materials testing. The selection, approval, qualification and maintenance of suppliers of starting materials, together with materials purchase and acceptance, must be documented as part of the pharmaceutical quality system (PIC/S Guide to GMP, Part 1, Chapter 5).

Manufacturers of finished products are responsible for testing starting materials in accordance with the product specifications (Chapter 5). They can utilise partial or full test results from the approved starting material manufacturer but must at a minimum include **identification testing** of each batch of starting material in accordance with Annex 8 of PIC/S Guide to GMP. However, identification testing alone would not be sufficient unless supported by comprehensive supplier approval processes (as outlined in Annex 8) and verification of all other quality attributes in the certificate of analysis (C of A). Identification of starting materials for active microbial ingredients provides assurance that the correct probiotic strain is used during manufacturing.

The TGA's expectations in relation to the requirements for starting materials in the PIC/S Guide to GMP are explained below in section **5.2** *Quality of starting materials* of these Guidelines.

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Version	Description of change	Author	Effective date
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