Complementary Medicines Australia
PO Box 450 Mawson ACT 2606
02 6260 4022
technical@cmaustralia.org.au

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Complementary and OTC Medicines Branch
Medicines Regulation Division | Health Products Regulation Group
Australian Government, Department of Health and Aged Care

Consultation Submission (Part A): *Guidelines for the Quality of Listed Probiotic Medicines*

Complementary Medicines Australia (CMA) appreciates the opportunity to provide feedback on the draft *Guidelines for the Quality of Listed Probiotic Medicines*.

CMA is the peak body representing the complementary medicines sector supporting Australian jobs, research, manufacturing and exports by meeting community demand for preventive and complementary healthcare. CMA represents approximately 80% of the supply chain for complementary medicines, including sponsors, manufacturers, suppliers and retailers.

CMA supports safe and responsible use of products, whilst retaining widespread consumer access and choice, through regulation that is balanced, transparent and cost-efficient.

CMA response

CMA thanks the TGA for the extensive efforts in the production of the draft guidance. We appreciate the time involved and the information provided to clarify certain legislative arrangements such as default standards.

CMA supports proper and adequate regulation of probiotics and is supportive of the TGA producing a suitable Probiotics Guideline that is applicable to current technology limitations. Presently, the correct species or strains are added to formulations and the TGA approved manufacturers ensure finished products meet appropriate regulatory and quality requirements through:

- supplier validated processes (for strain identification where required), and for all received materials - species identification by the receiving finished product manufacturer through in-house and pharmacopeial testing as required;
- applying GMP validation requirements such as blending validation;
- ensuring manufacturing conditions such as controlling temperature, formulating with low water activity ingredients to ensure the finished product meets stability expectations;
- meeting currently accepted global label expressions demonstrated by the total count at end of shelf life equalling the label claim of the total quantity of probiotic strains/species in the formula, except for any variability attributable to methods; additionally

- storage conditions in manufacturing facilities meeting usual GMP expectations to help ensure appropriate stability of the raw materials.

Most of the matters of concern raised in this submission do not relate to the above. Matters raised are either a concern from an administrative or legislative or labelling perspective, or more importantly, are expectations over and above what is technically and commercially possible and reasonable at the present time for the industry both globally and domestically for lower risk, multistrain/multispecies probiotic products.

CMA recognises and appreciates that some methods have been included in this guidance which respond to the normal and longstanding accepted practices around approaches to confirming quality of probiotics. Nonetheless this submission identifies a number of areas which we are concerned contradict the ability to use those methods or where it continues to be unclear what the expectation in practice will be, and which therefore may not effectively alter the potentially disastrous impact on the sector foreshadowed without equivalent consumer benefit compared to the existing market. There are many products available in the market, the direct benefits received by consumers from probiotics has fuelled growth. If all sponsors and manufacturers are meeting acceptable baseline expectations as mentioned above, this is a greater regulatory goal to achieve – by ensuring products across the marketplace are essentially similar in delivering expected quality – than the review of a small number of products against expectations that are unrealistically high or may not be commercially achievable but whose end difference to the actual product ultimately being delivered and therefore to the consumer is low or minimal.

There is therefore some ongoing concern that the guidelines continue to have elements that risk excluding the practical development of a number of multistrain probiotics in Australia. As per the above, CMA supports there need to be controls on probiotics including multistrain products, but within reasonable and achievable limits. There are specific benefits and value to multistrain products and consumers will continue to seek them whether here or elsewhere.

In order to bring adequate attention to the priority of different concerns in this submission, we have labelled each comment with a priority level corresponding to the map in Table 1 below. The matters raised in this submission follow the same structure as the Draft guidance document.

Table 1. Priority map for concerns raised in this submission.

Ideal	Important	Critical
Identified changes are considered ideal for efficient operation and clarity of the guidance, but where the issue is unlikely to have a significant impact on operations.	Identified changes are considered fundamentally necessary for best regulation and correct understanding of reader to the identified requirements. Non-resolution of the identified issues may result in impedance of best use of the guidance document, or result in misunderstanding of required expectations, or misapplication of principles on matters of key importance.	Identified issue or changes are required to align legal arrangements and best regulation. Non-resolution of the identified issues will result in one or more of the following: insurmountable barriers for industry market participation by creating high regulatory impact, high impact on consumer choice, prevent correct use of the regulatory framework by stakeholders, inadvertently cause non-compliance due to legislative incompatibility, or other critical issues.
Legislation not currently fit-for-purpose		
The addition of this to a response denotes sections where the draft Guideline is reinforcing concepts or requirements that are not fit-for-purpose due to legislative anomalies and lack of legislative updates, or a need for an update to supporting systems such as the ARTG. This creates conditions that are counter-productive, confusing or contradictory with impacts on both industry and consumers. In some cases the legislation may be fit for purpose, depending on interpretation.		

Overall Structure & Format

The overall structure and format is very long and complicated, duplicative, and has multiple cross-references. While this may be intended to help, the effect is that it makes it a difficult document to read and navigate, especially when a number of the underlying concepts can be dealt with in a simple and succinct way or in a single section. Tables are helpful to summarise information, the proliferation of large amounts of tables is generally not helpful.

CMA proposed early in discussions that any document is kept relatively short, simple and focussed on key relevant matters. This is what we generally mean by clarity except in a few circumstances where a particular concept requires additional exploration. We highlight this return to the ideal of a more succinct document, across all areas members express a strong preference for this. Similar consultative successes in focussing documents have occurred in some circumstances in the TGA Advertising area that have also been broadly supported by participating members of the TGACC

For example, the introduction of the Quality control part could mention relevance to safety and efficacy but whole sections on Safety and Efficacy in this part are unnecessary and venture into concepts and legislation unrelated to quality.

Section 5 in particular makes the document unnecessarily long and detracts from key focus on probiotics. Many readers of this document will be already familiar with the listing system and legislation. We suggest that information about legislation in this part could effectively be incorporated into the relevant corresponding sections of Section 4, reducing duplication where it is probiotic specific information, and general information can be removed from the document where it is relevant to all medicines and for which there are equivalent guidances elsewhere that can be linked to (such as the ARGLMRCM documents or TGA webpages.)

Finally, it comes across as very odd that this document assumes the responsibility for explaining in detail, base underlying concepts such as Ministerial standards and default standards which are relevant to ALL therapeutic goods and which are not specific to probiotics. The intended helpfulness of the author(s) is appreciated, however, for stakeholder clarity and good quality document management, the TGA need to take coordinated control of how information is managed across the organisation. Rather than an in depth exploration of standards application in a subset of medicines that is another subset of medicines, a guidance document about default and ministerial standards central to all medicines may be appropriate, with a cross-reference to that document in the probiotic guidance when general level information needs to be referred to. The current TGA guidance is a webpage that has not been updated in over 12 years and does very little to explain application of standards. https://www.tga.gov.au/resources/resource/guidance/compliance-ministerial-and-default-standards

Also see comment 4.1 b of this submission.

In summary, CMA supports:

- Removing or incorporating general information in Section 5 into general TGA webpages or ARGLMRCM documents that can be cross-referenced in this document
- Summarising any necessary information specific to probiotics in Section 4 instead of Section 5.
- Removing duplicative concepts or wording that reduce readability and clarity.
- A more hierarchical TGA approach to information where new detail about standards and their application relevant to all medicines is included at a higher level document that sub-documents like this could refer back to when this general information is needed.

Ideal	**Important**	Critical

Compliance with Compliance with B.P./Ph.Eur 3053 LBP monograph

CMA have previously suggested that, due to the way this monograph may be interpreted, it could create unnecessary damage to the Australian probiotics industry, all or part of this monograph should be considered for exemption for Listed medicines only, for the purposes of the Act. Our European counterparts have confirmed that Live Biotherapeutic Products (LBPs) are not equivalent to probiotics and are not intended to be. European LBPs are high risk medicinal products, which in Australia is equivalent to Registered medicines that contain live microorganisms for treating or preventing serious diseases. The design of the LBP monograph was never meant to implicate products that are probiotics in Europe and which are the similar or equivalent item of commerce and

health support to Listed medicines. The unusual design of the Australian regulatory system which auto-adopts international standards operating under non-equivalent regulatory frameworks means that these kinds of problems can be encountered in the regulation of complementary medicines from time to time, and recognition of the unusual situation needs to be acknowledged and sometimes accounted for.

The final outcome of whether part of full exemption would be necessary relies upon the interpretation of the monograph in this guidance and in practice. Although we recognise that 'alternative' methods of compliance are outlined in the guidance in some parts, the methods quoted or implied as 'alternative' remain in the large part the main methods of compliance both in Australia and around the world. The industry is working on and variably incorporating various enhancements and advancements, but often these remain only complementary to, and not always a replacement for, existing methods as discussed in this document

CMA is of the view that the primary and long held methods need to be recognised as the primary method or an equally valid option, not as a secondary or alternative option, which does not prevent the industry or the document from encouraging the use of complementary or replacement advanced technologies as they increasingly come into use over the next years or decades.

CMA remain concerned that the way this guidance is worded in some parts lends doubt and therefore creates regulatory risk to the use of the 'alternative methods', and creates confusion as to whether such methods can be reasonably employed without regulatory consequences: in particular, requirements about strain level identification and quantification in the normal manufacturing context.

Provided that reasonable expectations for regulatory and quality are met for all products, as described above in the introduction, CMA are of the view that the industry are meeting regulatory obligations and must be permitted to continue operating which permits the time and development needed for the additional methodologies to develop both globally and commercially within Australia.

If this cannot be done due to how 3053 LMB monograph is interpreted, then we consider that exempting all or part of 3053 must remain an option for consideration if unnecessary impacts causing the removal of health products for industry and consumers who value them is the result.

Ideal	Important	**Critical**
Legislation not currently fit-for-purpose (depending on interpretation)		

Document maintenance

There are many, many highly specific references in this guidance to a wide range of default standards, Ministerial standards, and other documents. All of these documents are complex and updated on a semi-regular basis. The need for maintaining this document as it currently stands would be regular and complex. The TGA and industry ran into this problem in one of the TIWGG working groups in respect of maintaining complex GMP technical guidance relating to the PIC/S code which is also updated on a semi-regular basis. For efficiency of document maintenance, the group decided to take a simplified approach. Not all of the probiotics guidance can be simplified in the

same way, however this is another perspective favouring greater simplicity where it can be warranted.

Ideal	Important	Critical

2. Scope

a. Paragraph 3: We understand the usual practice is to refer to other documents while minimising summarising or paraphrasing them, so that arising inconsistencies and the need for updating are limited. In our view, this is preferred, unless unavoidable.

Ideal	**Important**	Critical

b. Consideration of reference to excluding prebiotics in addition to postbiotics could be considered. Reference to synbiotics, usually a prebiotic and probiotic together, is likely unnecessary here as they are the combination of two different ingredients in product.

Ideal	Important	Critical

3. Quality control

a. The structure and content of Section 3 seems haphazard or unclear as to the purpose. Most parts come across as unnecessary (see individual comments below) as they could be introductory or would be better included in the technical section (Section 4).

It is not clear why Quality Control is called out specifically for probiotics. The general "Quality for listed medicines" guideline already covers all Quality related to a product. This section should only call out anything specific for probiotics that is different to general listed medicines.

Section 3 would be best as an introduction to quality and an introduction to relevant legislation in a very brief way with links to external guidance such as Quality for listed medicines. This way the reader encounters the core information and links before entering unified information in Section 4.

Removal of most of the existing sections of Section 3 is supportable, as per the below comments.

Ideal	**Important**	Critical

b. Listed medicines are not sterile. Therefore, with the exception of sterility, it is unusual for a guidance document to emphasise some parts of the quality definition.

c. Figure 1 might be considered unnecessary. Quality relationships with safety and efficacy are inherently understood.

Ideal	Important	Critical

d. Purity is not absence of impurities. Pharmacopoeial monographs and TGA compositional guidelines allow for impurities.

In relation to the parameters 'composition' and 'purity', the guidance also refers to *unintended* microorganisms and states or implies the absence of them. This is also problematic as all non-sterile medicines, including probiotics, are not expected to have an absence of other microorganisms (unless they are 'specified microorganisms').

There is a framework for microbiological control set out by the TGA's Microbiological Standards for Medicines Order (TGO 100). The TGO 100 does not refer to unintended microorganisms, it refers to 'specified microorganisms' and 'objectionable microorganisms' both of which are defined in the TGA Acronyms and Glossary[1].

It is also unclear if the reference to 'specified contaminant microorganisms' in this guidance is meant to be synonymous with the TGO 100's 'specified microorganisms'. If yes, we promote that the terminology is aligned to prevent confusion.

Overall, we support removal of unique terms that are similar but different to other TGA information, and alignment of the guidance with the TGO 100 and associated information.

Ideal	Important	**Critical**

e. It appears that the whole of Section 3 may be trying to impliedly introduce (through discussions on safety, stability, bioburden, unintended microorganisms and eligibility for listing) a concept equivalent to the term 'objectionable microorganisms', which is defined by the TGA Acronyms & Glossary as: '*In relation to guidance on microbial quality of prescription and over the counter medicines means: A microorganism that is not specified in Therapeutic Goods Order No. 100 - Therapeutic Goods (Microbiological Standards for Medicines) Order 2018, or in the default standards, but which might pose a risk if it is present in a medicine*.' If this is the intention, it would not be evident to the usual reader. Similar to the other items in Section 3, we question if it is necessary to include it here or if it should be incorporated, if necessary, into technical sections in Section 4. Particularly as the presence of objectionable organisms would be a quality issue, not an eligibility for listing issue. It would only be eligibility for listing if the sponsor was purposefully using a different ingredient to the one permitted in the Determination, which in almost all cases would need to occur at the species level – this is unrelated to objectionable organisms. Also see related comment at 3.2.1. c.

Ideal	**Important**	Critical

[1] https://www.tga.gov.au/resources/acronyms-and-glossary-terms accessed 17 August 2023

3.2 Safety

a. Section 21A(5) of the Act is summarised in the draft as 'the medicine must not harm any person' which is taken out of context of this part of the Act. Section 21A(5) of the Act is more specific in that it relays that if a person breaches *a condition of listing*, it is an offence if that results in harm or injury to a person, which has a different specific meaning to the one outlined in the guidance.

Ideal	**Important**	Critical

b. The sentence beginning 'Controlling the quality parameters…' is confusing or unclear as to its meaning and intent. Even a medicine with lack of quality control on some aspects does not mean that the end result is a non-permissible ingredient, or therefore that it becomes ineligible for listing.

For example, an unacceptably high decline in count before end of shelf life is a quality issue, but does not equate to a non-permissible ingredient or ineligibility for listing.

Suggest that this part is removed and the underlying concept being communicated is better communicated later in the document (Section 4). See related comments below at 3.2.1 a & c.

3.2.1 Bioburden

a. It is unclear why bioburden has its own subheading in Section 3, when other quality parameters do not. It appears out of place. It is also unclear why this part is referring to bioburden specifically - bioburden is not more or less important than other factors relating to quality. Discussion of the term should also be consistent with the TGO 100 and monographs. Any relevant matter relating to microbiological standards including undesirable organisms can be discussed in the relevant part of the technical part (currently Section 4.)

Ideal	Important	Critical

b. Confusingly, part 3.4 (Stability) later includes some explanation about bioburden in terms of unsafe levels of specified contaminant microorganisms. It is significantly concerning that bioburden is emphasised in 3.2.1 and 3.4, but that these parts, and the rest of the document, **never refer to the relevant legislation that is the TGO 100 and relevant monographs**.

Bioburden discussion must be kept consistent with TGO 100 and relevant monographs. It is unlikely the TGA going to take regulatory action on bioburden outside of TGO 100 and relevant monographs, or at least, if they were to, we do not know what form of action this would be. It remains unclear why Bioburden is raised without any reference to the particular applicable standards. Also see comment (e) of this section regards eligibility for listing comments.

Ideal	Important	**Critical**

c. There is duplicative information about the Section 26A(2)(b) certification that is given in 3.2. Support removal for readability.

Ideal	Important	Critical

d. This sentence also refers to the paragraph 26A(2)(f) certification about complying with prescribed safety criteria, but does not explain what that is. Prescribed criteria refers to the secondary legislation the Therapeutic Goods Regulations 1990, which does not prescribe safety criteria for listed medicines. Support removal of reference to 26A(2)(f) as it is not relevant at the current time, therefore will confuse readers as they will never be able to find the prescribed safety criteria.

Ideal	Important	**Critical**

e. This section also repeats concepts related to safety and eligibility for listing raised in 3.2, which is unclear, and unnecessary. Introductory paragraphs about safety and efficacy as relevant to quality should be sufficient to cover the topic without duplication.

   If there is a technical concept the TGA is trying to communicate in respect of the emphasis on eligibility for listing related to the Permissible Ingredients Determination, it is unclear what the issue is, but it may appear to be impliedly referencing a concept that is equivalent to *objectionable microorganisms* – this is unlikely to be evident to the general reader.

   In almost all cases, the Permissible Ingredients Determination permits ingredients at the species level, any minor change to an organism at strain level would not result in a change at the species level, so it is difficult to perceive the real risk that this communication is trying to manage. The approved species are safe organisms with a long history of use, where it is extraordinarily unlikely that variations of strain could pose a safety issue, which is the basis of species level (rather than strain level) regulatory acceptances around the world for foods, dietary supplements, natural health products, complementary or lower risk medicines.

Ideal	**Important**	Critical

3.3 Efficacy

CMA appreciates recognition that efficacy could be attributed to a species or higher taxon, and that if a probiotic medicine's efficacy is not strain 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. Please see comment on Figure 3, Line 5/6/7.

Ideal	**Important**	Critical

3.4 Stability

a. Stability also seems out of place in Section 3, confusing and duplicative when there is more discussion of stability in Section 4. This kind of information could be introducing (or incorporated into) the technical part around stability in section 4.6.

b. The discussion about unsafe levels of contaminant organisms seems unnecessary as the control of any listed or registered medicine for contamination is subject to the TGO 100 and relevant monographs, which is a commonly understood core concept to medicines/listed medicines. The parts that need to discuss TGO 100 and separately, already discuss stability in Section 4, are sufficient to cover this.

   We are concerned the sentence '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' implies testing that is different to TGO 100. TGO 100 and associated guidance is what is applicable.

Ideal	Important	**Critical**

4. Demonstrating compliance with legislative requirements

This way this part is written is very confusing. In particular, because it suggests some approaches don't need justification and other 'alternative' approaches do. However, the approaches that are given as 'alternative' in this document are actually the primary approaches used in Australia and largely around the world, other approaches are only being newly and cautiously implemented and usually only complementary to, not replacing, the primary (in this document, 'alternative') approaches.

Also see introductory remarks: Compliance with B.P./Ph.Eur 3053 LBP monograph.

Ideal	Important	**Critical**

4.1 How to determine which quality standards to comply with

a. Section 4.1 begins with a discussion of, and then includes a table instructing, which default and ministerial standards to comply with, before the concept of standards is introduced to the reader – standards are discussed in detail later in the document in Section 5. While we recognise that the guidance structure seems to be applying the 'inverted pyramid' approach under the Government Style Manual, it is nonetheless confusing to have no context to the discussion. A brief introductory sentence, and link to a later part of this document or external documents would be welcomed for clarity.

Ideal	Important	Critical

b. Section 5 of this document is the only TGA document to go into great detail on standards, when the standards apply to all therapeutic goods. A more informative approach to describing standards and the application of them (other than the TGO 101 guidance) is timely. However, Listed probiotics are only a small subset of listed medicines that are another subset of all medicines. It comes across as incongruous from a Government communications perspective, to introduce this detail applicable to all medicines, within a guidance for a very small subset of medicines. If a hierarchy system of communication is used, this broader information could more effectively be available in a central document (an improved or new guidance) discussing default and ministerial standard. This guidance can then link to it in various places including the beginning of section 4.1, instead of being the first document to include the explanatory detail applicable to all medicines.

   An additional risk of not taking the hierarchy approach to communication is that the compliance of other types of medicines or Listed medicines may be interpreted by TGA officers using the principles described in Section 5 of the probiotics guidance, when other sponsors who do not sponsor listed probiotics may not be aware of such descriptions, and therefore may be unfairly disadvantaged.

   This would shorten the probiotics document and focus it is specifically on probiotics. Our membership have strongly indicated an preference for a succinct guidance with only direct subject matter.

Ideal	**Important**	Critical

c. This part includes '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.' This appears to be addressing the issue of whether the Ph.Eur/BP 3053 LBP monograph is applicable to listed probiotics or not. However, as mentioned in the introductory part, it is not about the whether the monograph *does* apply technically due to the particular way it is worded, it is about whether it *should* apply based on the complex interaction between distinctly different regulatory systems layered with the complexity of auto-adopted default standards from other jurisdictions in Australia, and the commercial environment.

Ideal	Important	**Critical**

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

a. This Table does not clarify whether, or how, QBI interacts. We are given to understand from discussions with TGA directly that QBI is a suitable alternative to the strain enumeration statement in the Ph.Eur./BP 3053 LBP monograph. However to the reader, Table 1 does not resolve, but rather reinforces, the ongoing tension about Ph.Eur./BP 3053 LBP monograph and QBI, which has been a key tenant of discussion, because it is not clear in this central table or anywhere in Section 4 that alternative methods of compliance including QBI are available.

E.g. If compliance with Ph.Eur/BP 3053 LBP monograph at strain level enumeration in a multistrain blend, which most sponsors cannot achieve in the current commercial environment, compliance with Ph.Eur/BP 3053 LBP monograph cannot be achieved. The ability to use alternative methods of compliance including QBI need to be referenced and made clearer in this part.

Ideal	Important	**Critical**

b. For Tablets & Capsules – Option 1. For all options also see comment 4.a. above.

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 **final product**? *	✓ If YES, comply with the individual monograph and Ph. Eur./BP 3053 LBP monograph and Division 2 of TGO 101, OR Division 3 of TGO 101 and Ph. Eur./BP 3053 LBP monograph

This section requires compliance with more than one monograph for the Division 2 reference. It should include "as interpreted in accordance with the General Notices section", to be consistent with the wording of the Act where there are multiple applicable monographs within a single default standard.

Ideal	Important	Critical

c. For Tablets & Capsules – Option 2.
i.

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 LBP monograph	

The TGO 101 is indifferent to whether a more specific general monograph exists in a different default standard. Therefore, the GO 101 is indifferent as to whether the Ph.Eur. / BP has a more specific general monograph than the USP, for probiotics.

Under TGO 101, sponsors may comply with Division 3 and the General Chapters of the USP-NF, irrespective of anything, including whether there is an individual monograph for the product or the ingredient, or whether USP-NF 64 applies, or whether Ph.Eur./BP has a more specific general monograph. This part must reflect TGO 101's permission to comply with Division 3 and the General Chapters of the USP-NF.

Ideal	Important	**Critical**

ii.

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 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

This may be clearer?

✗ If NO, comply with Division 2 of TGO 101 and the individual monograph and the general chapters of USP-NF as interpreted in accordance with the General Notices section, OR Division 3 of TGO 101 and requirements relevant to the tablet or capsule in the general chapters of the USP–NF (but not USP–NF 64)

✓ If YES, comply with Division 2 of TGO 101 and the individual monograph and the general chapters of USP-NF as interpreted in accordance with the General Notices section, OR Division 3 of TGO 101 and requirements relevant to the tablet or capsule in the general chapters of the USP-NF (including USP–NF 64)

Ideal	Important	Critical

d. For dosage forms that are not tablets or capsules

i.

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 YES, comply with the individual monograph and Ph. Eur./BP 3053 LBP monograph

It should include "as interpreted in accordance with the General Notices section", to be consistent with the wording of the Act where there are multiple applicable monographs within a single default standard.

Ideal	Important	Critical

d. For dosage forms that are not tablets or capsules (continued)

ii.

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 YES, is the probiotic labelled as conforming to USP–NF?		

✓ If YES, is the probiotic labelled as conforming to USP–NF? (AND ✗ If NO, comply with Ph. Eur./BP 3053 LBP monograph)

We do not agree that the requirement to label as conforming to USP-NF should be interpreted or upheld as the ideal or correct application of standards for the following reasons:

- Label declaration of conformity in the USP-NF is particular to its home country, the USA, where compliance with the USP-NF is voluntary. Constructing a product to the USP-NF standard therefore requires label declaration in the USA to differentiate itself from other products. A statement that it is compliant with the USP-NF may be seen as a marketing advantage and therefore may also stimulate increased applications to the USP-NF for the inclusion of new monographs. Either way, it is specific to the USA regulatory approach.
- In Australia, the ad hoc declaration of compliance with the USP-NF on some products is liable to cause significant confusion or may cause misunderstandings (e.g. that one

product is superior to another), due to the lack of knowledge generally regarding therapeutic standards in Australia or elsewhere.

- In Australia, a series of Ministerial and default standards apply to *all* therapeutic goods including listed complementary medicines (which are categorically equivalent to dietary supplements in the USA). There is no need to declare compliance with *any* default or Ministerial standard for Australian products within the Australian regulatory approach, so to recognise and include this approach for USP-NF only is distinctly at odds with the Australian regulatory framework.
- The declaration of compliance with the BP or USP is a historical peculiarity only seen on vintage products that were around before the existence of a national regulatory authority in Australia. Declaration of compliance with the USP-NF would be nonsensical as consumers do not know what it is. Writing out the full name 'United States Pharmacopoeia – National Formulary' would also seem bizarre to the average Australian consumer.
- The TGA has adopted the default standards as *quality* standard, not a *labelling* standard. This should be reflected in the early TGA documentation when default standards were first adopted, but this is not available in the public record that we can find.
- Section 13(2) of the Act outlines that where a Ministerial standard and a default standard are inconsistent in their requirements, the requirements of the Ministerial standard apply. The Therapeutic Goods Order No. 92 - Standard for labels of non-prescription medicines does not prescribe *partial* labelling requirements. The TGO 92 is intended to be a *comprehensive* standard covering all elements mandatorily required on Australian labels. From this perspective, any **additional** labelling requirements in default standards should be **disregarded as inconsistent** for the purposes of Section 13(2). The labelling requirements in default standards are designed to be particular to the regulatory frameworks and expectations in their respective countries or jurisdictions, which does not include Australia.
- Ad hoc adoption of default standard labelling requirements from international jurisdictions on some Australian labels, but not other similar products (because those products fall under a different default or Ministerial standard) creates a situation that is the *exact opposite of the purpose of a standard*: it creates **non-standardised** labels in Australia rather than standardised ones. The competent authority must necessarily consider this.
- If the default standards happen to include one or more requirements that should be adopted in Australia, they should be considered for inclusion within the TGO 92 with proper Australian stakeholder consultation.
- As far as we are aware, a requirement for pre-assessed OTC medicines made according to the USP have never been required to include that they conform with the USP on their labels.
- Ph.Eur./BP 3053 LBP monograph 'Labelling' section comparably includes a requirement that the label states the name of any stabilisers and other excipients; which the TGO 92 is also silent on, however, that has not been raised in this guidance. It would also be considered a non-standardised anomaly if it were to be expected on some Australian labels but not others.

Interpretation of 13(2) and inconsistency

There is some possible variance in how the term "inconsistent" is defined and applied in practice.

Which interpretation has never been clearly elucidated either way by the TGA publicly to our knowledge. Based on member reports, members have received different information from the TGA over different times in response to enquiries on this specific issue about whether to label as USP-NF compliant. Older/longstanding advice from the TGA that the requirement to label as USP-NF was interpreted as *not* required, but it is not clear if this was a legislative response or simply an enforcement-discretion response based on common sense. More recent advice (equivalent to this draft) has been that non-labelling with the USP-NF meant that the standard did not apply or did need to be complied with (unless otherwise required by TGO 101).

Possible interpretation 1 (supported by TGO 101 Guidance and prior COMB practice)

Ultimately, one interpretation of 13(2) is, the complete and comprehensive nature of the TGO 92 labelling requirements disregards the need for any product to pick up other default standard requirements, or be labelled as compliant with USP-NF. If a product is not labelled as complying with USP-NF, sponsors still have the option of complying with the applicable quality parts of the USP-NF.

Possible interpretation 2 (supported by this draft guidance and some current COMB practice)

The other interpretation of 13(2) and 'inconsistent', which is that implied by this guidance, is that the TGO 92 must specifically outline an *equivalent but different* requirement in order for the default standard labelling requirement to be disregarded. In this situation, it must be recognised by all that therefore, the TGO 92 is currently not fit-for-purpose because, as noted above, it is out-of-context, archaic, confusing and non-standardised for some product labels to state compliance with USP-NF where many other product labels stay silent on compliance with anything. CMA will raise this in the TGO 92 consultation in view of the fact that this may be the interpretation taken, in which case the TGO 92 would need to specify that compliance with default standards does not need to be included on Australian labels.

Ideal	**Important**	Critical
Legislation not currently fit-for-purpose		

d. For dosage forms that are not tablets or capsules (continued)

iii.

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 YES, is the probiotic labelled as conforming to USP–NF?~~	✗ If NO, comply with Ph. Eur./BP 3053 LBP monograph	

CMA and other therapeutic industry associations have maintained to the TGA that a sponsor should have the option of choosing *which* default standard compendium to comply with for finished products, for numerous reasons:

- Different regions supply finished products to Australia, whether they are prescription medicines, OTC medicines, or complementary medicines. A USA supplier is not going to purchase and become familiar with the Ph.Eur or BP, they are in the USA, they work to the USP-NF. Similarly, European or British suppliers are simply not going to work to the USP-NF. Sponsors of products are beholden to their suppliers, and requiring regions to work to the standards of different regions is unrealistic.
- Purchase of compendial volumes, particularly the Ph.Eur./BP, are very expensive. Individual monographs cannot be purchased.
- Compendial volumes and the application of General Notices etc, have a great deal of information, sponsors/manufacturers should only be required to become familiar with one compendial volume.

The TGA has listened to industry on these issues in the production of TGO 101, which fairly permits sponsors and manufacturers to choose which compendial volume to conform to by creating a great deal of flexibility: the first choice which is to comply or not comply with an individual monograph, and the second choice (if not complying to an individual monograph) the ability to choose which pharmacopoeia's general monographs to comply with.

In CMA's submission to the TGO 101, we submitted that the TGO 101 needed to be expanded to cover all dosage forms for a variety of reasons, including this. This hasn't been actioned to date, and this issue with probiotics brings the matter to a head due to the apparent requirement to comply with Ph.Eur./BP 3053 LBP monograph if there is no individual USP-NF monograph.

To be fair and equivalent to TGO 101, sponsors of products that are not tablets and capsules should equally have the option to comply with the general chapters of the USP-NF rather than forced to use the Ph.Eur/BP 3053 LBP monograph.

This guidance unfortunately reflects legislative issues that haven't been dealt with. CMA continues to support, principally, the development of a standard similar to TGO 101 for other dosage forms, in order to deal with this very significant discrepancy in the therapeutic goods framework. In the absence of this work being done, it remains unreasonable and unfair to foist unworkable standard applications on industry via guidance, due to the TGA choosing to only partially addressing this issue legislatively to-date (for tablets and capsules only).

We submit it is far more critical to resolve the legislative issues (TGO 101 equivalency, TGO 101 itself, TGO 92) than to reinforce them through pushing through unworkable guidance.

Ideal	Important	**Critical**
Legislation not currently fit-for-purpose (depending on interpretation)		

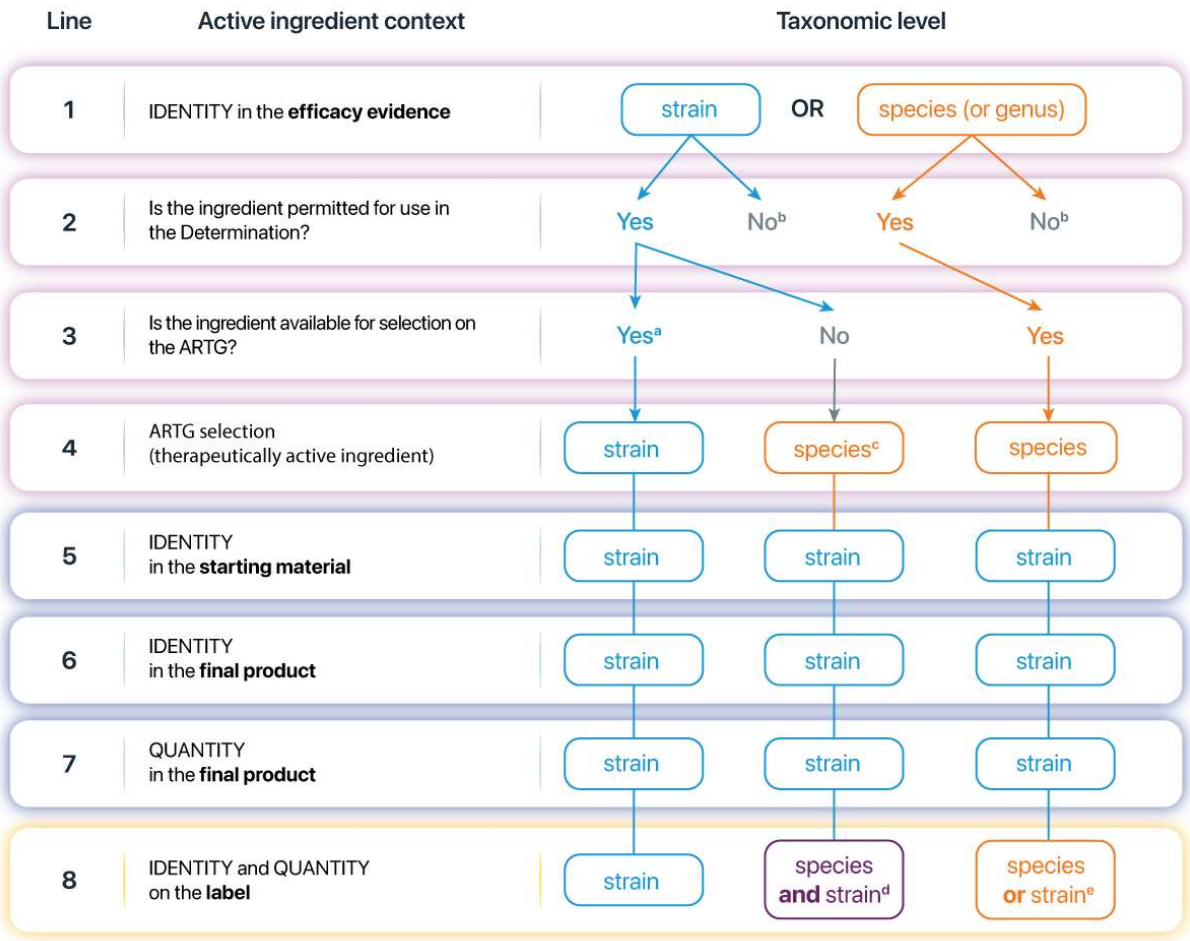
4.2 Taxonomic level for identification, quantification and labelling

4.2.1 Microbial Taxonomy

This part states that *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)*. This conflicts with the TGA naming protocols (AANs), the ARTG, and the TGO 92. Currently, the regulatory system regulates at the species level. Sponsors who include information about the strain are doing so voluntarily. For this reason we also disagree with the statement that *Generally, strain-level identification is important for all probiotics, whether they are single-strain or multi-strain*.

Figure 1. Taxonomic level of the active ingredient

Comments on each line of Figure 2 are included below:



[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 Error! Reference source not found. ***Error! Reference source not found.***.

[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 LBP monograph; or if there is a relevant USP–NF monograph that states the labelling is to be at the strain level. Refer to **Table 1**, Error! Reference source not found.,

The Identification column of Table 11 is not particularly helpful as it outlines recommended requirements, not mandatory requirements. See CMA's position below.

> The Quantification column should not be included at all. The TGO 92 requires a quantity for *each ingredient* in the formula, which is inconsistent with the USP which requires a 'total formulated enumeration'.

Table *2* and section Error! Reference source not found. ***Error! Reference source not found.***.

[e] Identity and quantity on the label should be at strain level (*Genus species* strain) if the relevant monograph is Ph. Eur. 3053 LBP monograph. **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,** Error! Reference source not found.,

The Identification column of Table 11 is not particularly helpful as it outlines recommended requirements, not mandatory requirements. See CMA's position below.

> The Quantification column should not be included at all. The TGO 92 requires a quantity for *each ingredient* in the formula, which is inconsistent with the USP which requires a 'total formulated enumeration'.

Table *2* and section Error! Reference source not found. ***Error! Reference source not found.***

Response:

Line 2: Strains are not outlined in the Determination, with the exception of one strain for Bacillus coagulans (MTCC) 5260 or 5856. Therefore, everyone using this table using strain-level evidence other than these 2 strains will have to answer "no" to this question. E.g. if whether Lactobacillus acidophilus LGG is permitted for use in the Determination (it is not, only Lactobacillus acidophilus is), which then gives the reader with L. acidophilus LGG or other strains the **incorrect advice** to *Apply for the new substance to be included in the Permissible Ingredients Determination*. Those using strain-level efficacy for a species that is already permitted in the Determination are **not** required to put in a new substance application for the particular strain, that is a ludicrous and entirely unsupportable suggestion.

Line 2 could say "Is the **species** available for selection on the ARTG"?

Ideal	Important	**Critical**

Line 3: Line 3 could say "Is the **strain** available for selection on the ARTG?". The right hand (orange species column), should skip over Line 3 altogether – the arrow from Line 2 should directly point to Line 4. It isn't relevant to answer Line 3 for species, as it is already answered by Line 2.

However, it still isn't clarified by the consultation or the TGA that strains would become selectable. Is this the case by the time this Guidance is published, and if so, when will that be consulted? Consultation on the guidance should not be occurring if other changes are afoot which are not being consulted upon. The guidance creates a precedence for the future changes without actually consulting them, which is not accepted Government practice. It must be crafted for the existing system, and if the system is updated in the future, the guideline should be updated then. It is confusing, redundant and unnecessary to include a flow chart with options that aren't possible and aren't relevant. Essentially, Line 3 shouldn't exist at all.

Ideal	Important	**Critical**

Line 4: Note (c) gives incorrect information because it implies that the Determination must specifically approve the strain (presumably in Column 4 of the Determination), in order for the sponsor to be permitted to select the species on the ARTG. This would lead to sponsors believing that they cannot select a species on the ARTG unless the strain is mentioned in the Determination. In the vast majority of cases, individual strains are <u>not</u> individually approved under each species in the Determination. As per above, sponsors are permitted to use strain-level evidence <u>and</u> are able to validly select the species on the ARTG.

Ideal	Important	**Critical**

Line 5,6: As previously communicated by CMA, finished product manufacturers in Australia only have the commercial and technical capability to identify an incoming ingredient at the **species** level, not the strain level. Finished product manufacturers rely on the supply chain and supplier qualification procedures to verify the strain, usually as part of a master/seed lot approach, it is not independently verified by testing in the raw material or the finished good. This table implies strain level identification by the FP manufacturer would be required, including on receival of the raw material by the finished product supplier and in the finished product. This is not possible and as it currently stands risks the probiotics industry in Australia without need.

Ideal	Important	**Critical**

Line 7: This is essentially still ruling out enumeration to genus level in a multi strain probiotic. Earlier in the document it is stated that evidence can be to species or even genus level. If evidence is to genus level, enumeration should be allowed to genus level. If this is not accepted, any multi strain probiotics with more than 2 strains per species will need to be cancelled from the ARTG.

When CMA enquired about an exemption from Ph.Eur./BP 3053 LBP monograph (the monograph which raised the issue of strain level enumeration), the COMB response was that it '*wasn't considered necessary given alternative strategies (such as use of QBI) to comply with the outcomes expected in Ph.Eur./BP 3053 LBP monograph are allowed. This is explained in section 5.6.2.1 of the Guidelines.*' However, it is not evident in this table that QBI or other alternate strategies are permitted, more importantly it does not recognise that these common strategies used globally as the standard (e.g. plate count method) do <u>not</u> quantify at the strain level but rather at the species, genus, or total count level. Leaving this table as-is states or implies to the reader (whether industry or TGA compliance officers) that quantification must occur at the strain level, which is not correct and does not reflect the reasonable situation for quantification.

Ideal	Important	**Critical**

Line 5,6,7 Although a product indication can be attributed to genus>species, this guidance expects identification and quantification to strain level for both raw material and final product. If efficacy is due to genus>species, testing should also be allowed to reflect this. The USP also allows this, so Figure 2 is out of alignment with the USP-NF.

Ideal	Important	**Critical**

Line 8: The purple box requirement to label the strain AND the species on the label is contrary to the TGO 92 labelling order which only requires the species. Guidance can only interpret legislation within reasonable bounds. It is not the role of guidance to set new labelling rules. A requirement to include the strain has not been required before and is not a part of any

TGA legislation except for *B. coagulans* and as mentioned above, the conflict with the TGO 92 and variability on how labelling suggestions in default standards have applied across ALL listed and registered medicines is a major cause for concern.

Further, the purple box in Line 8 would require the TGO 92 to be fixed to allow voluntary declaration of the strain as part of the ingredient name. Before that time, publication of this information will lead to misunderstandings that the strain must be in the ingredient name, which will lead to inadvertent noncompliance with TGO 92, directly caused by this guidance.

Further, Note D suggests that even if strain-level evidence is being used, the label only has to state the strain if it is required by a quality standard, which will result in more uneven labelling requirements based on the lack of using an Australian standardised approach but rather adopting ad hoc labelling requirements from other documents which are uniquely based around consideration of their own local NRA frameworks. Equivalent to comment for Table 1. d. iii. above, the quality standards in Australia were only ever intended to be adopted for quality purposes only and have never to our knowledge in any situation been regarded as a labelling standard. The comprehensive set of TGO 92 Australian labelling requirements override any labelling discussions within quality standards, which are known to be peculiar to their own jurisdictions (USA, or Britain/Europe).

Ideal	Important	**Critical**

4.3 Quality of starting materials

a. Table 4 is not applicable if the sponsor is applying Ph.Eur./BP 3053 LBP monograph or any other monograph potentially representing a mixture or blend (per Table 1), in which case section 13(4) of the Act states that the default standard that is applicable to one or more of the ingredients or one or more of the component parts does not apply in relation to the goods. This means Table 4 would not apply if 3053 is being used, and potentially, if other monographs are used or introduced (such as a potential USP multistrain monograph).

Ideal	Important	**Critical**

Table 4 also has the same issue outlined in comment Table 1 d. iii. Relating to manufacturers from different regions not using the pharmacopeia of a different jurisdiction.

b. CMA recognises that the information after Table 4 is intended to be helpful, however, we support its removal other than a very brief introduction and links to GMP guidance for the following reasons:

- The information is not specific to probiotics, it is relevant to all listed medicines
- Duplication or paraphrasing of some guidance in other guidances is highly undesirable unless absolutely critical (e.g. the allergens issue for Schedule 1 of TGO 92 may be an exception to the rule).

- The guidances referred to are very carefully worded, and several of the guidances are under active review.

Ideal	Important	Critical

Identification at the strain level

4.2.2 Summary of taxonomic level for identification, quantification and labelling

Section 4.2.2 states that:

> 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 Error! Reference source not found.).

It is not suitable that the taxonomic level for the active ingredient is based on the quality standards that apply to the product. Table 1 and Table 4 do not clarify this either. Further, it is not clear what this would mean in practice – if the quality standards are to dictate the taxonomic level of the ingredient rather than the regulatory framework and the AAN list, is this a suggestion that they also reverse-mandate other regulations in spite of conflict with those regulations?

Default standard (quality standards) requirements are submissive to the role of national regulatory authority (NRA) in each country; this is reflected in the standards. The default standard does not override the regulations, it does not dictate the taxonomic level selected by the NRA, instead, it is secondary to, or intended to be harmonious with, that which is already decided upon by the NRA. For example;

- FDA does not require strain-level compliance, rather, strain-level identification outlined in the USP-NF is voluntary for those products who voluntarily decide to comply with the USP-NF, and in some cases species level is suitable.
- EMA require strain-level compliance but only have products equivalent to registered/prescription microbial medicines, which are not called probiotics, but are called Live Biotherapeutic Products (with the equivalent monograph) to distinguish them from probiotic products. Probiotics in the EU are largely governed by EFSA who regulate to the species level.

Australia is unfortunately an “outlier”, because we adopt systems from other countries that haven’t been designed for our regulatory system. Therefore, the Act has numerous built-in mechanisms to override or exempt monographs or parts of monographs that are not suitable to our system where these problems arise. Rather than adopting monographs or systems that are unsuitable, create a non-standardised approach, or seriously damage Australian industry and therefore consumer access,

it is incumbent on the NRA to utilise the mechanisms in the Act that allow these anomalies, inconsistencies with the Australian framework, and inappropriate applications of standards to be harmonised with the ability of the industry to operationalise and which are suitable for regulation.

This has been done on a number of occasions. There are existing exemptions for default standards and Orders such as the TGO 101 and TGO 100 (Australian standards hierarchically superior to the international default standards) clarify how default standards should be applied in the Australian context, and subsequently prevent or exempt manufacturers from complying with unreasonable or impossible circumstances.

Strain level requirements are not part of the TGA regulatory framework generally and the quality standards should not dictate the TGA's regulatory system in reverse. In Australia, sponsors mostly use strain level taxonomy and labelling voluntarily (currently excepting Bacillus coagulans and the Column 4 requirements). If a product has evidence at a species level and has a species selected on the ARTG from the AAN list, there should not be the expectation for them to have strain-level identification and quantification due to quality standards such as the Ph.Eur/BP 3053 LBP monograph which was not designed for this category of goods, rather the *mandatory minimum* would apply to species level identification and labelling where that is the level of the evidence used.

This document should also not imply that lack of a strain in the Determination requires a new substance application, if the species is already in the Determination. There is risk of this through the document, especially in Figure 2 and related parts.

Where strain identification is used, it generally follows the seed/master lot system which deals with characterisation as set out by Ph.Eur./BP 3053 LBP monograph, which is why manufacturers rely on supplier qualification of raw materials at the strain level for identification. This also deals with the apparent concerns around objectionable organisms as controls ensure they are not present in master or working seed-lots.

Ideal	**Important**	Critical

4.4 Active ingredient identification in the final product

At finished product manufacturers in Australia, identification to the strain level cannot usually be commercially performed, or newer strain methods may act as complementary to traditional methods. It is an evolving field which highly depends on the manufacturer and the labs and. Finished product manufacturers identify to the species level on receipt of active ingredient raw materials. The species level is the level included in the Permissible Ingredients Determination that is permitted for use in Australia. Finished product manufacturers use supply chain validation for verification of the strain. This is consistent with Ph.Eur./BP 3035 LBP monograph. If the TGA considers or has confirmed that it is not, then that part of the monograph needs to be exempted.

Section 4.4 is self-contradictory by stating or implying in numerous areas that identification must be done to the strain level (by the finished product manufacturer), but it also appears to reluctantly give the ability to identify the active ingredient strain by using validation through the supply chain.

Section 4.4 also references and duplicates information given in Versions 2.0 and 2.1 (current) of the *PE009, the PIC/S guide to GMP for medicinal products TGA interpretation and expectations for demonstrating compliance*, made in July 2020 and September 2020 respectively which provides specific discussion about probiotics. Neither the prior versions (Version 1.0 in 2017 and the preceding TGA webpage Q&A) are available on either the TGA webpage nor the National Archives of Australia for stakeholders to view. Nonetheless, it is clear that the information about probiotics was added in V2.0 July 2020 because it specifically references the Ph.Eur./BP 3053 LBP monograph which was only published in April 2018 and made effective in April 2019.

CMA has searched our records 2019 and 2020.and can confirm that we were never consulted about the additions to the regarding probiotics during this time. During this time TIWGG conducted a Gap Analysis to which CMA responded in regards to Cross contamination as referenced in Clauses 3.6 and 5.18 – 5.21, including the key points that:

> In these clauses there is references to cross contamination and production in segregated areas (required for products such as penicillins, live vaccines, live bacterial preparations and some other biologicals). CMA notes that 'organisms from active substances' could be interpreted as including Probiotics, but that Probiotics have for many years been manufactured and packaged in facilities that also manufacture other products for human oral consumption, including tablets, capsules, powders & liquids. Except for some specific low humidity requirements for manufacturing some Probiotic products, it has been normal practice to manufacture Probiotics in the same facilities as other oral products, with appropriate cleaning being conducted based on a risk management approach and in accordance with appropriate validation exercises.
>
> While CMA fully understands that it has been a long-standing requirement that highly sensitising materials such as penicillins and cephalosporins are manufactured in separate dedicated manufacturing facilities, CMA seeks assurance that these clauses will not be interpreted to similarly require separate manufacturing facilities for Probiotics for oral consumption, which have long been accepted as beneficial human gut bacteria. Live vaccines are generally modified and/or partially inactivated strains of human pathogens and again any arguments for separate manufacturing facilities for such products should not be extended to include Probiotics containing beneficial bacteria for oral consumption.

Subsequently we received a summarised response from the TGA on 25 March 2020 that the Question and Answer document would be edited to clarify that probiotics for listed medicines may continue to be manufactured in shared facilities where existing controls are sufficient.

The additional part on Quality Control (Chapter 6) that this guidance refers to, was added without any further specific consultation or notification to CMA or other stakeholders on the change and inclusion to this part.

Testing of probiotics

Probiotic therapeutic goods and their active ingredients are expected to be manufactured and controlled in compliance with all Default Standard monographs relevant to the goods, including general and specific monographs including. "Live Biotherapeutic Products for Human Use" (Ph. Eur. 3053), BP Appendix XVI H. Microbiological Examination of Live Biotherapeutic Products, (Ph. Eur. 2.6.36 & 2.6.38).

It is expected that an identification test be performed on every container of probiotic raw material received by a medicinal product manufacturer.

Identification testing

The identification test selected should be discriminatory and allow correct identification of 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 e.g. 16S rRNA sequencing, PCR etc.

Where the product label claim is for a particular genus or organism only, traditional biochemical methods may be suitable for identification purposes.

Our concerns with this unconsulted addition are:

- Parts of it are already inconsistent with this draft guidance.
- Probiotics are not expected to be controlled under "all default standard monographs" nor is Ph.Eur./BP 3053 LBP monograph applicable to all goods, as recognised in this draft consultation guidance, and as set out in section 13 of the Act:

  (7) For the purposes of this Act, in working out at a particular time if therapeutic goods conform with a default standard applicable to the goods, if:
  (a) after applying subsections (2) to (5), 2 or more default standards are applicable to the goods at that time; and
  (b) at that time, the goods conform with at least one of those standards but do not conform with at least one of those standards;
  then the default standards that the goods do not conform with are taken not to apply to the goods at that time.

- As previously discussed, listed medicine probiotics are by definition, not intended to be LBPs which are a specific high risk medicinal category in EMA, and in spite of the generic definition, the designers of the monograph made the monograph with this in mind – refer to the submission by the EU group that CMA provided to TGA in 2020. Registered probiotics are equivalent to LBPs and it is appropriate for the 3053 in full to apply to Registered LBPs in Australia.
- Genotypic identification methods e.g. 16S rRNA sequencing, PCR etc, are not widely commercially available in Australia for probiotics.
- Genus only label claims aren't permitted, the regulatory framework /AAN list / TGO 92 requires species.
- Traditional methods are the methods employed for incoming materials, even when the strain level is claimed, except in perhaps some exceptional circumstances. As mentioned earlier, strain characterisation and confirmation is through supplier processes in most cases.

Due to the numerous issues with the PE009 guidance, it needs to be reviewed concurrently with this guidance, and this guidance could not refer to it or its content, until the review is complete due to the inherent issues with that guidance.

Ideal	Important	**Critical**

4.5 Active ingredient quantification in the final product

a. This section needs to be shortened. It is long and unnecessarily complicated; manufacturers are capable of understanding how to quantify the products based on the technologies they have access to. Paragraphs 3, 4 and 6 are unnecessary except 'Sponsors should choose a strategy most appropriate for their circumstances' – also comments in Table 5 below.

b. This section should be premised with an acknowledgement to current monograph methods (plate count) used for over 125 years, and the limitations and variability as per USP and BP descriptions. To meet requirements for strain level quantification, sponsor would need to validate alternative methods, which may not be commercially available at this time.

c. Paragraph 5 refers to using QBI 'provided… it is capable of demonstrating the quantity of each strain in the final product'. This part of the sentence confuses things because when QBI'ing per section 4.5.3, it is impossible to objectively demonstrate the quantity of each strain in the final product after it is blended. There are ways that the quantity of each strain can be reliably predicted or surmised, *but this is different to definitively demonstrating it.* In our previous submissions we have mentioned the drafts were confusing due to apparent contradictions in terms – this is another part that appears to the reader as a contradiction-in-terms or an impossible expectation.

Ideal	**Important**	Critical

d. Section 4.5 and Table 5 both contradict Figure 2 of the guidance. Figure says that species or genus level efficacy requires

Table 5

a. Table 5 is unnecessary. It also confuses things without any particularly useful purpose in the document. For example, a sponsor can aim to test to the highest taxa in any scenario if there are validated methods available. Therefore, there may be individual situations where the testing permits a higher level taxa quantification than the minimum specified in the Table under "Compliance expectations." However, for all scenarios specifically Scenario 2, 3 & 4, the acceptable baseline minimum is following QBI and total count or genus count for stability.

Ideal	**Important**	Critical

b. Multistrain and multispecies products cannot comply with the 'Compliance expectation to be 'quantitatively tested' at the strain and species level respectively. The 'Compliance expectation' in Scenario 3 and 4 are impossible to comply with for most multistrain products under current commercial circumstances in Australia. **Scenarios 3 and 4 can currently only be quantified by QBI and for stability purposes, tested by culture methods at total count.**

Enacting the compliance expectations in this table would wipe out the multistrain products on the market without equivalent consumer need or benefit.

Further, the information in this table contradicts the information given immediately preceding the table about being able to use QBI.

If Table 5 is retained, to be consistent with practice, to not seriously damage the Australian manufacturing industry without need and to be consistent with other parts of the document (e.g. QBI), it must be referring to quantification and methods for 'Compliance expectations' rather than testing and taxa level.

Ideal	Important	**Critical**

4.5.1 Selecting and validating quantification methods

a. The guidance discusses that '*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.*'

This is presumably with a view to meeting the **individual strain enumeration** requirements for Ph.Eur./BP 3053 LBP monograph. In Australia, these techniques are not presently being employed and should not be presented as the main method of compliance. We are not aware of labs that can and do use the above methods, including the TGA labs.

The view that these should be used as the preferred approach also remains at odds with other regulators. Companies whom have picked up additional methods such as flow cytometry internationally, are using them as a secondary analysis and not as a primary means of satisfying company or regulatory expectations. They are not considered suitable for, and cannot replace culture methods, at this time. In the USA, the FDA has on principle accepted the use of CFU (culture method) as a quantitative method suitable to be reflected on a label, but have refused to accept the use of other quantitative methods including those based on flow cytometry (FDA).

The current monograph methods for enumeration are plate count, which are not capable of quantifying to strain level, therefore, these methods remain the 'alternative methods' and should not be referred to or implied as the preferred or primary methods.

This part of the guidance also discusses culture methods and implies they are inferior or an alternative method. In Australia, the culture method is the only method available at this time, and as for other countries, remains the primary method suitable for pharmacopeial, labelling and regulatory obligations. Even if an updated quantification approach could theoretically be taken for a label, CMA has previously raised the issue of lack of correlation of new methods with the 100+ years of evidence for probiotics based on culture methods, something that the TGA haven't responded to and for which there is no equivalent relief in this draft.

In such an environment, it is not the role of a regulator to imply novel methods that are rarely available as the preferred methods, and to imply that accepted, long-held method as an alternative method.

Importantly, this part then states that "*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 labelled stated content*." There is no way to definitively demonstrate this at the strain level under culture methods – please also refer to comments on section 4.6 in this submission. Stability on the final count and considering stability data on individual strains or blends remains the commercially achievable best practice and is universally considered adequate to accept the presence of strains in blends at the expected quantity at the end of shelf life. While there are some elements of the draft guidance that potentially recognise this method, there are other paragraphs or sentences that deny the ability to do it (such as the sentence above and section 4.6), which creates risk and confusion.

The culture method needs to be recognised as the dominant and still only practicable method of enumeration in the finished product including multistrain blends. **Failure to adequately recognise or accept this in the guidance and accept this in post market reviews could have a catastrophic impact on the sector with no tangible benefit for consumers. The only beneficiaries will be overseas platforms selling multistrain probiotics imported for personal use, creating a net detrimental benefit to Australian manufacturing, Australian exports, and protection of Australian consumers.**

Ideal	Important	**Critical**

b. The document includes: 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'. These references aren't as useful (more for chemical tests) as the ones in the BP (Ph. Eur. general texts 5.1.6) and USP (1223 validation of alternative microbiological methods) for validation of alternative microbiological methods.

Ideal	**Important**	Critical

4.5.2 Assay limit for content; and 5.7.2.5 Not less than the stated content

Whether a product is in, or not in, the TGO 101, application of the pharmacopeial methods should be recognised and accepted.

The guidance again raises the concept of a **non-standardised** approach to products that are essentially equivalent in the delivery of their ingredients and intended health purpose, in the eyes of both industry and the consumer, through the communication that:

- **For dosage forms that are tablets or capsules** … ensure that the assay limit for the content of each active microbial ingredient in the final product is 'not less than stated content'; *vs*

- **For dosage forms that are *not* tablets or capsules,** …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.

For non-discrete dosage forms, application of pharmacopeial methods, which include analytical error tolerances, is permitted, but this is not permitted for TGO 101 Division 3. This is a non-standardised approach. For the purposes of content deliver, there is no difference between a probiotic powder in a jar and probiotic powder that is surrounded by a capsule or blended into a tablet, it is merely a matter of consumer preference and convenience. To create different standards for them is impracticable but also absurd. In the eyes of any competent authority, this is obviously a situation that needs to be rectified in order to create a harmonised standard.

Both USP-NF <64> and Ph.Eur/BP 3053 LBP monograph are applicable to **all** dosage forms and both refer to culture methods/CFU. USP <1223> Validation of alternative microbiological methods notes that microbiology is a logarithmic science. While we can distinguish between 100 and 1000cfu (a difference of 1 log10), **it may not be possible to discern smaller differences (less than 0.3-0.5 log10)**. "It is reasonable to consider that the typical level of precision will typically be on the order of 15%-35% relative standard deviation." Similarly, BP 3053 assay (and which is referring to culture methods) states "the potency of each strain… is not less that the stated value *or it is within the stated range*" and general provisions state "Limits for process parameters and for tests carried out during production and on the final lot may be in the form of maximum values, minimum values, or tolerances around a given value. Limits are based on the results found for batches tested clinically and those used to demonstrate consistency of production. These limits may subsequently be refined on a statistical basis in the light of production data."

The results from a CFU count (used for over 125 years and as part of most historical clinical trials) are a signal or estimate. Therefore, the CFU result should include a range for acceptance as an estimate of the true amount in the product. Sponsors at the same time must ensure methods are appropriately verified for their purpose as well as investigate any out of trend and out of specification results. Laboratory proficiency testing will help and this should also be identified in the guidance.

It must be raised here (and confirmed with the former TGA technical lead of the TGO 101 project, Ms JB), that the purpose of the TGO 101 Schedule 2 assay limits is to set a limit where there is no other standard available, it is not intended to exclude the application of pharmacopoeial methods, this is made clear by their incorporation into Section 8(2) of the TGO 101:

(2) The requirements in relation to a tablet or capsule for which there is no applicable monograph are:

(a) the Australian specific requirements; **and**

(b) the requirements relevant to the tablet or capsule that are specified in one of the following:

(i) the general monographs in the European Pharmacopoeia;

(ii) the general monographs in the British Pharmacopoeia;

(iii) the general chapters of the United States Pharmacopeia-National Formulary.

In interpreting section 8(2), it is necessary to consider the guidance in TGO 101 which states (bold emphasis added):

> 'Applying the requirements of an applicable monograph draws in requirements from both the specific monograph and the general monograph (or their equivalents) in the relevant pharmacopoeia.
>
> **Similarly, consideration of the general monographs of the BP or EP or the general chapters of the USP is necessary when applying the Australian specific requirements.**
>
> The requirements of the default standards apply except where the Order includes a conflicting requirement. Where the requirements are inconsistent, the Order takes precedence.'

The requirements of the Order and of the default standards are consistent in that they state the goal of having the stated content at the end of shelf life (i.e. they do not conflict), which CMA agrees is the intended outcome, however the default standards also allow in the methodology sections, the recognition of analytical error, which is not inconsistent or conflicting with the TGO 101 because the TGO 101 specifically makes the assumption in section 8(2) as recognised by the guidance that consideration of the general monographs or chapters are **necessary** (i.e. are accepted) in interpreting elements of the Division 3 Australian Specific Requirements.

Both USP-NF <64> and Ph.Eur./BP 3053 LBP monograph are applicable to **all** dosage forms. This is reflected in the microbiological methods (CFU plate counts) used. The monograph methods are based on sample weight, and *not* per tablet or capsule. The method is intended to apply to the sample weight of the material whether it is used in finished powders, tablets or capsules. Considered in totality, it becomes clear that the TGO 101 is intended to be used in conjunction with the pharmacopeial methods and that the methods are intended to also apply to tablets and capsules.

In prior communications about probiotics guidance, CMA has communicated that in during the TGO 101 consultation (2018), we did not raise the need for clarification of TGO 101 regarding analytical uncertainty because, the requirement for probiotics was not new or changing (it was continuous with the prior 10 years of the TGO 78), any matters surrounding probiotics were not specifically discussed in the TGA consultation documents, and more importantly, we already had written information from the TGA confirming that a **+/- 0.5log**

variance based on method variability was acceptable for the TGO 101 limits. If the TGA are changing the interpretation of the rules without agreement, against both the pharmacopeial acceptance methods and other internationally accepted methods, and not during a relevant TGO legislative consultation period, this remains unfair and unreasonable. It also sets in motion an illogical non-standardised approach for different dosage forms, and in turn potentially cripples parts of the industry, or may significantly raise consumer prices. This could lead to further challenges, including complaints on Government processes, and/or appeal mechanisms.

To resolve this ongoing dispute proactively, we seek appropriate resolution that is agreeable to all parties, through either appropriate ***legislative interpretation*** of section 8(2) of the TGO 101, in which the Schedule 2 assay limits are recognised in this guidance as being interpreted in conjunction with the pharmacopeial methods. If it considered by the TGA after legal analysis that this cannot be done, then the TGO 101 should updated to include ***legislative clarification*** in which it is specifically clarified that the pharmacopeial approach is acceptable in respect of Schedule 2, *OR* alternatively to recognise the previous written advice from the TGA confirming that a +/- 0.5log variance based on method variability is accepted.

The net effect should result in recognition of the appropriate methodology and approach for probiotics based on known analytical error for plate count methods that have otherwise been considered universally acceptable:

- The International Probiotics Association & Council of Responsible Nutrition document includes that 'Products should contain 100% of the quantity of probiotics declared on the product label at end of shelf life, except for any variability that is attributable to enumeration methods.' We agree with IPA and CRN.
- Weitzel et al. (2021) reflect that, while the means to further reduce analytical error needs to be explored, limits ranging from 0.2 to 0.5 Log10 for the critical difference between two tests at the 95% confidence interval can be found in international standards and national guidelines.
- Health Canada include that 'Licence holders should ensure that all products meet a minimum of 80% of the label claim for viable organisms at the end of the shelf-life.'

Ideal	Important	**Critical**
Legislation not currently fit-for-purpose (depending on interpretation)		

4.5.3 Quantified by Input

a. It also remains unclear to readers in this section, that QBI is an acceptable method of conforming to the Ph.Eur./BP 3053 LBP monograph. If it can be assumed that multistrain products which are subject to Ph.Eur/BP 3053 LBP monograph can comply with the enumeration expectations by applying QBI, that should be made clear here.

b. The TGA guidance on process validation doesn't refer to surrogate analytics, some have requested more clarification on this.

c. Water activity section implies the data needs to be specific to the organisms or product. Grouped/broader scientific justifications that are valid also need to be recognised.

d. This section discusses some concepts that are only relevant to QBI. The QBI section and section 4.6 need to be better harmonised for clarity. In addition, there can be and are reliable scientific assumptions made about the inactivated state of freeze-dried probiotics, which is not recognised by the section, the opposite is implied.

e. Reference to conducting total count as part of stability may be worth mentioning in the QBI section if it is expected.

4.6 Stability of the final product

a. This section includes:

> Stability data for active ingredients could be generated for individual strains, or combinations of strains, in conjunction with any other relevant information, such as total count or total count by genus. 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.

Probiotic strains are metabolically inactive. The way this paragraph is written is effectively stating that testing needs to be done to demonstrate a lack of interaction between strains/species when they are combined into a blend. These methods are not available. This data cannot be produced and cannot be tested by regulators either due to method unavailability. However, the metabolic inactivity of strains is well understood and well known. Provided stability data of the strain(s) (individually) and the blend/finished product (as a total count) is available, this is sufficient to justify the strain stability in the product, without producing additional data demonstrating lack of interaction between strains. If this expectation for individual data on individual strains in individual blends remains in the guidance, it will have a catastrophic but unnecessary impact on the industry as these expectations simply can't be met under current testing circumstances. The knowledge of the trend of the strain stability and the finished product stability in total, is sufficient.

Ideal	Important	**Critical**

b. The next paragraph goes on to state:

> 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.

The way it is written is such that testing needs to be done. As per the above, this is a massive undertaking that is effectively impossible to meet with a multistrain/ multispecies formula. Viability of these studies are completely commercially and economically impractical. It is an insolvable problem and inclusion of these kind of regulatory expectations will most definitely cause unnecessary impact on the sector and consumer availability with no effective difference to product quality and outcomes. A number of members emphasised that this was the most concerning addition to the guidance, and that it needs to be removed altogether as there was universal agreement that is unviable to conduct such studies.

The steps discussed earlier including control of stability and control of water activity, are sufficient to affirm that the microorganisms are metabolically inactive in the container. Provided that the manufacturer understands the trend of the organism under the storage conditions and that they can stand up to these conditions, it is sufficient to use general literature or grouped scientific justifications to justify that there is no interaction.

Ideal	Important	**Critical**

4.6.1 Accelerated stability studies

The reference to accelerated studies as being unlikely to substantiate stability are assuming the study uses a typical chemical test approach as per ICH guidelines – suggest removing this line. This first paragraph needs some re-wording to present what is expected.

Ideal	**Important**	Critical

4.6.2 Grouping of on-going stability testing

The last paragraph includes:

> 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 Error! Reference source not found. *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.

It isn't clear what the expectation is here, if it is different to or the same as the preceding paragraph. If it is the same, we suggest deleting this paragraph for clarity. If it is different, it should be clearer what this part is asking for.

This paragraph also states *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.* As expressed previously, commercial probiotic strains in raw materials and finished products under the correct conditions are metabolically inactive. They are not growing and changing in the finished product. Some strains may decline at different rates to others, if this is the issue being expressed it should be expressed in these terms.

Ideal	Important	Critical

4.6.3 Overage

See earlier comments for 4.5.2.

4.7 Labelling

a. This section states that if *Ph. Eur./BP 3053 LBP monograph is an applicable standard, then **in addition** to the species name, the **strain** name ('Genus species strain') must also be on the label (Error! Reference source not found.)*.

   This is not true. As per 13(2) of the Act, if there is an inconsistent requirement in the Order, then the Order takes precedence over the default standard. The TGO 101 guidance also states that 'Where the requirements are inconsistent, the Order takes precedence.'

   There are two conflicting or inconsistent requirement in the TGO 92, which are that:
   - the TGO 92 specifically requires the AAN to be on the label, and the AAN is always a species name, it is never a strain name.
   - the TGO 92 9(3) does not permit additional text to be between ingredient names. Additional text includes the name of a strain, irrespective of Ph.Eur./BP 3053 LBP monograph.

   This does not preclude a sponsor from voluntarily including a strain name elsewhere on the label under current circumstances, but it does mean that it is not a *requirement* under Ph.Eur/BP 3053 LBP monograph for it be included in the ingredient name.

   Additionally, if a sponsor has included it after a species name in the ingredient list for consumer information, CMA is of the view the TGA should apply enforcement discretion in respect of the above two points of the TGO 92 because it is a reasonable and justifiable approach in spite of the rigidity of the TGO 92. However many sponsors would already by choosing not use the strain name in that location because it is different to the above TGO 92 requirements. It is contradictory for this guidance to *require* that the strain name is included in the ingredient name on the label when:

   - it would cause non-compliance with the TGO 92 and

- the default standard requirement is clearly overridden due to the TGO 92 and 13(2) of the Act.

Ideal	Important	**Critical**

b. The section also states '*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 (*

c. ***The*** Identification column of Table 11 is not particularly helpful as it outlines recommended requirements, not mandatory requirements. See CMA's position below.

The Quantification column should not be included at all. The TGO 92 requires a quantity for *each ingredient* in the formula, which is inconsistent with the USP which requires a 'total formulated enumeration'.

d. **Table *2*)**.'

The Identification column of Table 11 is not particularly helpful as it outlines recommended requirements, not mandatory requirements. See CMA's position below.

The Quantification column should not be included at all. The TGO 92 requires a quantity for *each ingredient* in the formula, which is inconsistent with the USP which requires a 'total formulated enumeration'.

Table 2. (Labelling part only)

Pharmacopoeia Section heading	Identification	Quantification
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.

CMA's position on proper labelling for listed probiotics:

Equivalent products to listed probiotics globally, including EFSA, Health Canada, and FDA, include the species name but may include the strain voluntarily. The EMA's Live Biotherapeutic Products and the equivalent monograph Ph.Eur./BP 3053 LBP monograph are not equivalent to Listed probiotics, they are only equivalent to Registered (including prescription) Live Biotherapeutic Products.

Australia should follow the naming convention that currently exists in Australia and around the world for equivalent products:

1. Mandatory naming of the species (already in place)
2. Voluntary naming of the strain where desirable or relevant is already occurring. However it should be openly recognised in Australia as permissible to do so, and it should not be actively prevented from being included in the ingredient list by the TGO 92 – which requires updating in this respect.
3. Mandatory labelling of the strain must not be required by either future updates to the TGO 92 or by existing application of the Ph.Eur./BP 3053 LBP monograph(which applies to some products only), as the sponsor may be relying on evidence for the species or the genus, in other words, it is nonsensical to require a strain name when it is irrelevant for consumer information and to the purpose of the goods. It would only cause the consumer to look for information on that strain or to compare products on strain names that is not of any relevance. This view is backed up by the USP <64> where scientific substantiation of health benefits that are not strain specific, probiotics may be labelled with the genus and species names.
4. It would be helpful for the guidance to clarify where the labelling requirements of the default standards do not apply because the requirements of the TGO 92 take precedence. If the TGA considers that only some labelling requirements of the default standards do not apply and others do, then, after all other matters have been resolved through any necessary updates to the TGO 92, then it would helpful and clarifying for sponsors to have a table outlining which label requirements specific to probiotics apply in Australia, e.g.

Label item	**Does it apply to probiotics supplied within Australia?**
Species name	Required by TGO 92
Strain name	Voluntary unless specified in Column 4 of 26BB
Declaration of conformance with USP-NF for USP-NF compliant products	Does not apply due to inconsistency with TGO 92.
Total formulation enumeration for USP-64 compliant products	Does not apply due to inconsistency with TGO 92.
CFU/g or CFU/serving for USP-64 compliant products	Does not apply to all products due to inconsistency with TGO 92, however CFU/g is an option to comply with 11(2)(i)(v) of the TGO 92 where the number of organisms present per metric unit for products that are liquids and powders must be stated.

Ideal	Important	**Critical**

5 Applicable legislation

Cohesive structures and streamlined information

CMA has reviewed the legislation and our membership widely and emphatically agrees that most, if not all, of Part 5 should not be in this document. The TGA must seek a coherent and streamlined approach to educational materials, with a top down hierarchal approach rather than extensive duplications and sub-documents including new information that other higher documents have not included.

We understand that work has been done in Section 5, however, any improvement to existing information must be incorporated into those existing other documents, not reproduced or re-invented in this document. Some information is already included in other TGA guidances which could be linked to.

TGA guidances are becoming lengthy and often duplicative without necessity, this must be avoided especially in documents like these which are a subset of other categories (listed medicines or all therapeutic goods). It is confusing to have similar but different information in different places, moreover, the inclusion of a great deal of general information in a guidance for a specific set of products reduces focus from the core subject, probiotics.

The following sections of Part 5 that are sufficiently covered in other TGA documents (the ARGLMRCM documents, or TGA webpages) and are considered duplicative or unnecessary to include in this guidance:

- 5.1 The Act
  - Also see comments on content of 5.1 in Part B of the submission, in particular, the objection to the unnecessary and rather threatening language about criminality and so forth, when this subject matter is sensitively and appropriately dealt with in other universal TGA guidance for all products under the TGA compliance hub.
  - Table 7 is perfect for incorporation into the draft TGA overview guidance for all listed medicines. It is unnecessary to be included here. However, references to the 26BB and 26BF Determinations should not be in the 'quality' section, they should be in a section about 'listing requirements'.
- 5.2 Listing certification
  - Also better for incorporation into the draft Overview guidance for Listed medicines and also currently covered in other parts of the ARGLMRCM.
- 5.3 Conditions of listing
  - Covered elsewhere in the ARGLMRCM.
- 5.4 Cancellation of listing
  - Although this is more specific to quality than some of the ARGLMRCM, it the latter that should be updated for all listed medicines, not included in this document.
- And any other parts that are generic, not specific.

Ideal	**Important**	Critical

References to 'legal consequences' and criminality

The references to legal consequences and criminality, including those that are emphatic or repeated, is considered language that is unnecessary, combative, and heavy-handed.

Criminal prosecution related to listed medicines is extremely rare (currently non-existent), and the likelihood of a criminal prosecution proceeding in relation to probiotics quality is also likely to be extraordinarily unlikely when considering Government guidance documents such as the *Australian Government Investigation Standard* and the *Prosecution Policy of the Commonwealth – Guidelines for the making of decision in the prosecution process*. The draft guidance therefore gives an implied threat that is considerably out of context for the reader with criminal prosecutor policy. This reinforces its unnecessarily threatening nature. It would be sufficient to have a general link relating to compliance to the TGA webpage guidances on *Compliance management* and *Compliance actions and outcomes*. For example, the prosecution policy includes:

> Having satisfied himself or herself that the evidence is sufficient to justify the institution or continuation of a prosecution, the prosecutor must then consider whether, in the light of the provable facts and the whole of the surrounding circumstances, the public interest requires a prosecution to be pursued. It is not the rule that all offences brought to the attention of the authorities must be prosecuted.
>
> The factors which can properly be taken into account in deciding whether the public interest requires a prosecution will vary from case to case. While many public interest factors militate against a decision to proceed with a prosecution, there are public interest factors which operate in favour of proceeding with a prosecution (for example, the seriousness of the offence, the need for deterrence).
>
> Factors which may arise for consideration in determining whether the public interest requires a prosecution include the following non-exhaustive matters:
> (a) the seriousness or, conversely, the relative triviality of the alleged offence or that it is of a 'technical' nature only;
> (b) mitigating or aggravating circumstances impacting on the appropriateness or otherwise of the prosecution;
> (c) the youth, age, intelligence, physical health, mental health or special vulnerability of the alleged offender, a witness or victim;
> (d) the alleged offender's antecedents and background;
> (e) the passage of time since the alleged offence when taken into account with the circumstances of the alleged offence and when the offence was discovered;
> (f) the degree of culpability of the alleged offender in connection with the offence;
> (g) the effect on community harmony and public confidence in the administration of justice;
> (h) the obsolescence or obscurity of the law;
> (i) whether the prosecution would be perceived as counter-productive, for example, by bringing the law into disrepute;
> (j) the availability and efficacy of any alternatives to prosecution;
> (k) the prevalence of the alleged offence and the need for deterrence, both personal and general;
> (l) whether the consequences of any resulting conviction would be unduly harsh and oppressive;
> (m) whether the alleged offence is of considerable public concern;
> (n) any entitlement of the Commonwealth or other person or body to criminal compensation, reparation or forfeiture if prosecution action is taken;
> (o) the attitude of the victim of the alleged offence to a prosecution;
> (p) the actual or potential harm, occasioned to an individual; (q) the likely length and expense of a trial;
> (r) whether the alleged offender is willing to co-operate in the investigation or prosecution of others, or the extent to which the alleged offender has done so;

(s) the likely outcome in the event of a finding of guilt having regard to the sentencing options available to the Court;
(t) whether the alleged offence is triable only on indictment;
(u) the necessity to maintain public confidence in the rule of law and the administration of justice through the institutions of democratic governance including the Parliament and the Courts;
(v) the need to give effect to regulatory or punitive imperatives;
(w) the efficacy, as an alternative to prosecution, of any disciplinary proceedings that have been found proven against the alleged offender to the extent that they encompass the alleged offence; and
(x) the adequacy in achieving any regulatory or punitive imperatives, of relevant civil penalty proceedings, either pending or completed, and whether these proceedings may result, or have resulted, in the imposition of a financial penalty.

Ideal	**Important**	Critical

5.6.3 USP–NF

a. The first dot point states that '• 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'.

This is **incorrect for tablets and capsules supplied in Australia**. It effectively gives the reader the advice that the product cannot comply with the USP if there is not an official article. This is reinforced by the information in Table 1, which says if there is no individual monograph for the final product or the ingredient in the USP for tablets and capsules, then the product must comply with 3053 TGO 101 permits compliance with general chapters irrespective of whether there is an official article.

The TGO 101 guidance states that:

> Monographs for dietary supplements in the USP are considered to be applicable monographs for the purposes of TGO 101.
>
> Medicines that do not have an applicable monograph in the EP, BP or USP must meet, at a minimum, the Australian specific requirements in TGO 101.

The TGO 101 includes:

The requirements in relation to a tablet or capsule for which there is no applicable monograph are:

(a) the Australian specific requirements; and
(b) the requirements relevant to the tablet or capsule that are specified in one of the following:
  (i) the general monographs in the European Pharmacopoeia;
  (ii) the general monographs in the British Pharmacopoeia;
  (iii) the general chapters of the United States Pharmacopeia-National Formulary.

Therefore, if there are no official articles in the USP, this does not prevent the sponsor from complying with Division 3 and adopting additional relevant requirements from the general chapters of the USP for tablets and capsules (if any). It also does not prevent (see 4th and 5th

dot point of this section of the draft guidance) a sponsor/manufacturer from justifying the use of principles or parts of USP-64 as part of in-house testing for products or strains that are not cited in a USP monograph.

Most importantly, the lack of official articles in the USP does not mean the TGO 101 mandatorily requires tablets and capsules to comply with Australian specific requirements and Ph.Eur./BP 3053 LBP monograph as stated by Table 1 or implied by this section.

The TGO 101 guidance says (bold emphasis added):

> If a medicine that is a tablet or capsule is subject to an individual monograph in the EP, BP or USP, the medicine's sponsor can choose to comply with any one of those, in conjunction with any specific requirements prescribed in the Order. Alternatively, the sponsor could choose to comply with the Australian specific requirements set out in TGO 101. **Meeting any one of these sets of requirements demonstrates compliance with TGO 101.**

Ideal	Important	**Critical**

5.6.3.1 Microbial contamination

This section does not discuss the TGO 100, which takes precedence over the microbiological standards in the default standards. This part must discuss TGO 100 as the required standard.

Ideal	Important	**Critical**

5.6.5 Relationship with ministerial standards

Issues with this part include:

a. Parts of the guidance state or reinforce requirements which are already inconsistent with Ministerial standards. These parts of the guidance must be removed to provide the correct information, to avoid inadvertent non-compliance, and to provide a reasonable level of clarity instead of conflicting information.

b. Strain names are not required to be stated on the label in accordance with Ph.Eur./BP 3053 LBP monograph, as the TGO 92 definitively contains inconsistent requirements (the requirement to label as per the AAN). AANs do not include strain names. This therefore **removes** the need to comply with the mandatory strain labelling in this monograph.

c. This section also states that 'strain names and quantities are to be stated on the label in accordance with … USP-64'. This suggests it is mandatory, however, it is only a recommendation as reflected earlier in the draft guidance.

d. Further, it is patently ridiculous for a competent authority to state that a product must do something that contravenes their own standard, and then to state it must be done in a way that doesn't contravene the standard, especially when the same legislative framework specifies that inconsistencies in the default standards are to be disregarded. Forcing product labels to do this doesn't help anyone in the community: industry, health care providers or

pharmacists or retail assistants, or consumers. It is absurd. Sponsors voluntarily naming strains have had to name them in a way that doesn't contravene the standard, but CMA has previously flagged this is an issue that must be fixed in the TGO 92 as soon as possible especially in view of the TGA's implied preference for strain name inclusion. It is role of the competent authority to identify and address labelling anomalies that do not serve the community, not to simply reinforce them because they exist. They only exist because these problems in the TGO 92 were not identified at the time at the time of consultation or drafting of that document.

Ideal	Important	**Critical**

5.7.1 TGO 92 – Labelling

This part is not required. All listed medicines should be following other standard labelling legislation and guidance including the ARGLMRCM and the Medicine labels: Guidance on TGO 91 and 92. Stating basic TGO 92 naming requirements is not required in this guidance. Earlier links to the TGO 92 are sufficient – this is the approach taken in other TGA guidance documents.

Ideal	Important	Critical

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

Similar to the above comment, the earlier links are sufficient and the section is not required.

It is confounding to state "*Consider whether other ministerial or default standards are applicable to different dosage forms (e.g. powders, oil drops [pearls], chewable tablets and gummies)*", because other Ministerial standards to not apply to these dosage forms.

Ideal	Important	Critical

5.7.2.2 Ph. Eur. or BP individual monographs

The content of this part is helpful however, it could be presented in conjunction with Table 1 and this section could be removed.

Ideal	Important	Critical

5.7.2.5 Not less than the stated content

This part does not need to be here, it is already discussed in 4.5.2. It is very confusing and time-consuming for the same concept to be covered repeatedly in different parts as the reader has to try to synthesise why the same thing is being discussed in a different way in multiple parts. Section 4.5.2 already covers the concepts in this part so this part should be deleted to reduce unnecessary duplication.

Ideal	**Important**	Critical

Transition periods

Transition periods are likely to be required for:

- Manufacturing changes. To be incorporated across a large range of products and a range of facilities, a period of 4 years is considered the minimum time required.
- Labelling changes. To be incorporated across a large range of products, 4 years is the time required, particularly if the sponsor has not previously collected strain information. Any changes to strain labelling must be made a priority for near term (2024) changes to the TGO 92, in particular the ability to add a strain name at the end of the species name in the ingredient list without contravening section 9(3) of that Order.

Transition periods need to be from the 'release for supply' date to allow on-shelf stock to be sold through.

