Technical Alert

Current Regulatory Understandings of Probiotics (Therapeutic Goods)

A number of questions have occurred regarding approach to probiotic products and compliance under the Therapeutic Goods Act. The below information is provided to members for information on our current understandings based on recent regulatory activities and discussions. Note circumstances may vary by case and that often compliance must be underpinned by justifications.

Compliance with Probiotics Labelling under TGO 92

Can I only state the Number of Organisms; or am I required to state the Weight AND Number?

May medicine labels for probiotics:

- only state the number of organisms; (for example, 1 billion organisms) OR
- must they state the number of organisms and the weight of the probiotics? (For example, 2mg and 1 billion organisms).

The TGO 92 *11(2)(a)* provides that for a solid dosage form such as a capsule or tablet, the quantity or proportion of an active ingredient to be included on a label must be expressed as the **quantity of the active ingredient**, *11(2)(b)* and *(c)* have similar requirements for liquids and powders. However, the term 'quantity of the active ingredient' as a term is not defined by the labelling order.

11(2)(i)(v) provides that **in addition** to the requirements of the above, preparations containing biological organisms must be expressed as the **number of organisms** present per dosage unit or metric unit depending on the dosage form.

Therefore, there was a question of whether 'quantity of the active ingredient' means 'weight', or whether it could mean 'number' – most dictionary definitions define quantity as weight or number. If it could mean number, then only the number needs to be declared on the label to satisfy both the requirements of 11(2)(a) and 11(2)(i)(v).

CMA provided in summary that:

- Considering that the weight of a probiotic can be difficult to accurately define, and can be affected by excipients, it is not practical or meaningful to include the quantity by weight.
- The literature and clinical experts only refer to the quantity by numbers, not by weight.
- The dictionary definitions support using the number as the 'quantity', if preferred.

Based on discussions regarding the above with the TGA, we understand that they are now willing to accept the "number" of probiotics alone as the expression of quantity (or alternatively, the weight and the number). Either approach would considered acceptable. However, we recommend that if you include the "number" only to include a note on your product file to support reasons why, in case this is questioned in any future post market review.

Can the number of organisms be expressed in CFU?

The TGO 92 *11(2)(i)(v)* requirement noted above refers to the number of organisms. After discussion, the TGA considers that stating the quantity of organisms in colony forming units or 'CFU' —rather than a count of cells, in the case of live probiotics—is capable of complying.

The TGA have also stated that in deciding whether to report CFU or number of cells ('organisms'), sponsors must however take care to ensure that what is stated on the label is supported by relevant evidence, is not misleading to consumers and is consistent with their ARTG entry. It would likely be misleading to report a number of organisms when what has been enumerated is CFU.

Enumeration and Stability considerations

Interpretation of the "Not less than" requirement

The TGO 101's Schedule and general monographs such as the European Pharmacopoeia require that the content of the medicine is not less than the stated (labelled) content, throughout shelf life. The TGA's microbiology section have provided that when enumerating probiotics, any count over the label claim is acceptable. If under, they only allow -0.5log – anything lower than this would be considered a fail.

Clarification is being sought on whether this would change if there is (in some circumstances) a quantity restriction on the probiotic organism in the Permissible Ingredients Determination.

Approach to quantifying by input, and stability data for mixed species of the same genera

Information from the TGA is that:

- It is preferable if sponsors are able to formulate products in such a way that the statement of content label claims can be robustly substantiated at the end of shelf life for each claimed species or strain by either a very scientifically robust justification for QBI, or preferably, molecular identification/quantification techniques; however, that
- Quantification by input is an acceptable method of formulating probiotics if more sophisticated methods of quantifying microorganisms in probiotics to species level are not readily available for quality control or stability purposes. In which case, it is acceptable to quantify microorganisms to the genus level by plate count methods following the formulation of the final product, due to the limitations in currently available methods.

CMA is seeking to stay aware of developments in molecular techniques for identification and enumeration that may affect the regulatory environment, and welcomes feedback from members as more information becomes available.

Grouping stability data where there are different strains in the reference product

The TGA provided that the use of stability data for a probiotic reference formulation that does not have the same strains as the newly developed product, is not sufficiently robust to support the quality and stability of the new product. 'Grouped' stability data was not accepted on the basis of different strains between two particular products. We note this view was formed in respect of a specific case, and that in a different case and with a robust grouping justification, they might form a different view. This becomes very case-by-case. In this circumstance, accelerated/extrapolated early stability data on the actual product was deemed acceptable. Again, such decisions might depend on the data itself and how this is justified in respect of the specific conditions/length etc of the stability trials.

In any case, it appears that if a sponsor decides to use grouped stability data from a product with any difference in strains, on the basis of a justification when releasing a new product, it would be wise to hold a strong justification and to start the product on its own stability trials as quickly as possible in case any grouping justification is later not deemed sufficiently acceptable by the TGA.

Members are encouraged to forward any identified issues to technical@cmaustralia.org.au for attention by the Committee Secretariat.

ENDS