CMA Submission to the TGA Consultation:

TGO 101 - Remaking Therapeutic Goods Order No. 78

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February 8, 2019

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Introduction

Complementary Medicines Australia (CMA) appreciates the opportunity to provide feedback on the Department of Health's Therapeutic Goods Administration (TGA) consultation documents:

- *Draft Therapeutic Goods (Standard for Tablets, Capsules and Pills) (TGO 101) Order 2019;*
- *Draft Guidance for TGO 101, Version 1.0 December 2018;*
- *Remaking Therapeutic Goods Order No 78 - Consultation paper, Version 1.0 December 2018.*

Our sector supports everyday preventative and complementary healthcare, both through clinical settings and individual self-management of wellbeing. International public health organisations include the WHO (World Health Organization) place ongoing emphasis on the important role of self-medication, including the use of traditional medicines. Due to increasing recognition and personal experience of individuals of the benefits that complementary medicines provide in assisting to maintain and enhance health, demand for complementary medicines has increased world-wide and will continue to grow.

Global attention to complementary medicines has brought increasing competition between national economies. As a world leader in the field, Australia attracts international demand for our high-quality products, in turn offering a disproportionally large contribution to exports and research in the field.

While manufacturing an essential to a diverse and resilient economy, it is recognised that Australia is a high-cost place to do business. Other manufacturing industries in Australia have suffered or moved off-shore due to the availability of low cost overseas production. Our sector's success to date has been built on recognised high quality standards tempered by a balanced approach to regulation, without excessive or restrictive levels of regulation that would cause unnecessary impediments to growth in the competitive global scene where we are already at a competitive cost disadvantage.

It is necessary for Australian consumers and economy that the Government implement balanced, flexible, and appropriate policy to maintain a local manufacturing environment and maintain Australia as a high quality supplier of complementary medicines to meet the ongoing demand.

Consultation

The document under review, the existing **Therapeutic Goods Order No. 78** (TGO 78) is intended for reissue as the upcoming **Therapeutic Goods (Standard for Tablets, Capsules and Pills) Order No. 101** (TGO 101). This document has one of the most significant effects on the requirements for tablets, capsules and pills, and therefore the activities of the manufacturing industry.

CMA notes the current consultation has been provided on a shortened timeline, which has not permitted full & transparent discussion of the scientific and policy basis of the additional proposals with the regulated industry. It is noteworthy that TGA has undertaken open and transparent consultation with industry in previous iterations of this document, TGO 35 and TGO 36, prior to their amalgamation into TGO 56, and prior to the introduction of TGO 78. These consultation processes have ensured that the resulting Therapeutic Goods Orders have provided relevant standards and meaningful guidance to both the industry and TGA.

CMA and other stakeholders originally expressed a preference early in the consultative process for a continuation of existing arrangements, until such time as discussion of adequate length and whole of Government approach could be considered through consultative mechanisms. Some of the additional requirements proposed for this document increase the level of regulation for the Australian sector, but are not consistent with key international approaches that have undergone expert deliberations.

CMA has held discussions with and sought comments from manufacturer members, who have raised significant concerns regarding the draft TGO 101. In particular, the proposed introduction of certain unique and different requirements, where they are not consistent with one of the stated aims of the revision, to "**create efficiency through increased international harmonisation**". CMA trusts that the current consultation process will result in TGO 101 providing an approach that is genuinely consistent with the relevant requirements of international standards as they are applied in practice.

Executive Summary

- ***Soft pastilles***. The proposed TGO 101 deals with 'discrete' dosage forms – capsules, tablets and pills, including vitamin, mineral and other complementary medicine substances. Soft pastilles (also known as 'gummies') are a discrete dosage form which also include these ingredients, therefore the exclusion of soft pastilles from scope is a concern. Consumers who purchase vitamin supplements may expect that the same quality standards apply across this category of goods. The manufacturing processes for pills and soft pastilles are very similar, it may be difficult to provide definitions that include pills but which exclude soft pastilles.

- ***Elemental impurities***. The introduction of uniquely different standards to international arrangements, particularly in relation to elemental impurities, has been identified as the primary concern. Of most concern is that the unique Australian requirements for heavy metals impose specific concentration limits on individual units, as distinct from the relevantly applicable international documents such as USP <2232>, which contain a different compliance goal and an appropriate range of implementation options. As international harmonisation has been presented as a major driver for the revision, it is difficult to understand why the introduction of different impurity limits with more limited compliance options is being proposed as a harmonisation measure.

  Significant additional costs have been identified requiring investment in Inductively Coupled Plasma Optical Emission Spectrometers (ICP-OES) and /or Inductively Coupled Plasma Mass Spectrometers (ICP-MS) laboratory instrumentation and associated running and personnel costs, to conduct the testing of individual dosage units as would be required in many circumstances by proposed TGO 101 even where it is largely redundant by international safety standards. This will largely increase costs for consumers and make Australia increasingly uncompetitive without fully analysed or balanced benefits to consumers. The pressure on contract testing laboratories is already significant and it is highly questionable as to whether such demands could even be met and whether therefore small and new manufacturing enterprises would be disproportionately disadvantaged under such a scenario.

The overwhelming position of CMA members was that new, unique, and non-harmonised international concentration limits for heavy metals per individual units as proposed in Schedule 1 is definitively not appropriate for the Australian specific requirements (for CMs without a specific FP monograph), however, that USP <2232> could be adopted in its entirety for listed complementary medicines, *provided* that a suitable transition time period is provided to account for this new increase in specific regulatory requirements.

Although regulatory assessments are necessary for any regulatory increase, if elemental impurity limits inconsistent with international documents that are directly relevant to the products in question continue to be included in TGO 101, members have indicated it will be critical that a full RIS (regulatory impact statement) is undertaken prior to TGO 101 being finalised.

- ***Residual solvents***. Ph.Eur for residual solvents is not generally applicable to listed medicines as a class. Complementary medicines use low risk Class 3 solvents as part of manufacturing – notably ethanol, at a rate that is the same or less than foods and can be approached through risk management, to not unnecessarily increase costs without benefit to industry or consumers.

- ***Modified release units***. The testing of sustained or modified release tablets or capsules for listed medicines, should not require a dissolution test, but a disintegration test conducted at appropriate pH levels to imitate gastric & intestinal contents. In addition, dissolution testing for multi-active tablets or capsules is generally not technically feasible or strongly supportable as a required measure except for folic acid.

- ***Alternative Standards***. Permitting alternative standards is not opposed, but the addition of cross-referenced requirements from other standards must be minimised unless determined to be necessary for matters of health and safety. This new and quite different system may raise implementation issues and require further consultation and amendments in the future.

- ***Late changes from consultation***. Any late changes to the consultation document unless specifically supported and that increase impact must not occur without further consultation and/or impact assessment.

Scope of TGO 101

Soft pastilles

CMA members have previously and continue to request that the scope of TGO 101 be extended to include soft pastilles (aka 'gummies'). Similar requirements and assay limits should be applied to soft pastilles, which have become an increasingly popular dosage form for consumers since TGO 78 was introduced.

In addition to concerns that there is no reason why soft pastilles containing vitamins and minerals should be excluded from the scope of TGO 101 that applies to other discrete oral dosage forms, the description of the pill manufacturing process in the consultation paper may not exclude soft pastilles being classified as pills. The consultation paper describes pills as being manufactured via wet massing and moulding techniques, which is also how soft pastilles are manufactured.

Recommendation – Scope

1. Reconsideration of applying TGO 101 to all discrete oral solid dosage units, including soft pastilles (gummies), or a description of relevant arrangements that allow for appropriate harmonisation.

Elemental Impurities

The Consultation paper - *Remaking Therapeutic Goods Order No. 78 - Standard for Tablets and Capsules and reintroducing pills into the remade Order* includes the below information (relevantly highlighted) includes the following:

‘Adoption of internationally-harmonised limits for impurities

Previously, the control of impurities in medicines was largely focused on quality controls placed on raw materials. Occasionally, specific impurity limits were included in the individual monographs for finished goods.

Recently the BP and USP both introduced heavy metal requirements into the general monographs for finished goods. These limits will apply to medicines citing compliance with an individual monograph in either of the pharmacopoeias. For consistency, it is proposed that suitable limits are included for all tablets, capsules and pills.

Addition of these limits to the existing TGO 78 requirements, to create updated Australian specific requirements, does not impose significant new regulatory burden on sponsors. Compliance can be established in a number of ways. For example, it may be appropriate to use results generated under existing testing requirements for impurities in raw materials rather than routine testing of the finished goods to demonstrate compliance.’

‘Impurity limits for herbal preparations

The BP and the USP have used different approaches to determine acceptable elemental impurity levels. In particular, there is a considerable discrepancy between the BP Herbal Drugs monograph and the USP ⟨2232⟩ Elemental Contaminants in Dietary Supplements monograph. This may reflect the different legislative frameworks in which herbal medicines and dietary supplements are regulated in each jurisdiction.

In this consultation, we are seeking feedback in the most appropriate limits to apply to herbal-based medicines not following an individual monograph. Two proposed options are presented within the draft Order: option 1 – arsenic, cadmium, lead and mercury limits based on those in the BP; and option 2 - arsenic, cadmium, lead, total mercury and methyl mercury from the USP.’

CMA notes that the Australian specific requirements as they are proposed in Schedule 1 of the draft TGO, for both listed medicines generally (item 2) and herbal products (item 3), are not harmonised with the approach and options provided within key international reference documents, and will create significant new burden on manufacturers and sponsors without meeting harmonisation goals.

The testing for the specified concentration limits in finished products will result in many manufacturers / sponsors needing to invest in Inductively Coupled Plasma Optical Emission Spectrometers (ICP-OES) and /or Inductively Coupled Plasma Mass Spectrometers (ICP-MS) laboratory instrumentation. The cost of purchasing such instrumentation, together with the associated running costs, including both reagents and trained laboratory personnel will be a significant additional impost on the industry which is already at maximal regulatory burden in terms of laboratory space and personnel to meet the demand of consumers and the needs of sponsors to create a varied and cost-effective range of products.

The proposal which will result in price increases for consumers for little to no effect on quality or safety for the vast majority of products. In short, the proposal in its current form is not a practical and aligned approach in protecting consumers, is untenable for the sector, and would require a full Regulatory Impact Statement that we predict would unlikely be justifiable.

Consumer safety

The ICH and the USP have the same requirements for permitted exposure for the elements lead and cadmium. They are stricter than those applied by Canadian requirements. As strictest requirements, there is no driver for the Australian government to put in place high burden requirements different to standards developed by international expert committees. The USP <2232> (*in its entirety)*, is the only document designed to capture complementary medicines as a product category (US 'dietary supplements') including herbal products. It sensibly applies requirements to inorganic arsenic, and has low limits for lead, cadmium, mercury and methyl mercury.

Lead has been an item of increasing interest and concern. Sources of lead in Australia include tap water; air pollution; food; toys; cosmetics; and older housing stock causing lead dust, lead in soil, etc – some sources which are rarely risk managed in any meaningful way. The question arises of how the Government is managing and balancing risk across industries for heavy metal exposure for the Australian population. We note that the complementary medicines industry currently risk-manages elemental impurities through raw materials to ensure consumer safety, with a low risk profile for

background sources of possible exposure in a landscape with variable lead requirements for all industries and sources, particularly common high exposures such as water and housing.

In discussing new specific requirements therefore, it is not necessary to provide requirements that diverge from internationally accepted approaches for these relevant product categories. Both the United States Pharmacopoeia and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) apply an exposure limit which is **4-5x less** than the permissible amount of lead intake that Australians may consume from drinking water alone, when determined by the Australian Drinking Water Guidelines and NHMRC Nutrient Reference Values. Therefore, the ICH/USP limit for lead are the tightest that could reasonably be discussed for materials of natural origin, and far lower than many other background sources of lead that the Australian population is regularly exposed to.

Due to the existing risk management strategies employed by the industry, the vast majority would not exceed the tight, but internationally harmonised limits. This is a core regulatory reason for not applying an additional onerous and restrictive subset of requirements and compliance options for Australian manufacturers, with resultant price rises for consumers and complications for international trading to an industry that is already one of the safest in the world and where there is not an established problem of magnitude in order to do so as outlined in Government guidance for making regulatory policy.

Existing proposal requires reconsideration to meet international alignment.

The two key international documents outlining expectations for elemental impurities by the ICH and the USP both require conformance with a permitted exposure in the medicine, whereas the TGO 101 proposal only aligns with one possible option out of the four options provided by the ICH documents and none of the three options from the USP. This is extremely restrictive in scope relative to both the ICH and the USP, documents that have both undergone considerable consultation by international expert committees.

Consultation Option 2 for herbal preparations proposes limits that on face value look similar to the USP <2232>, but are significantly different. Consultation Option 2 proposes concentration limits for

finished product, whereas the USP <2232> does not apply those limits to finished product but to individual components (ingredients) in only one of the three options for meeting the pharmacopeial standard.

The BP requirements are somewhat reflected in Consultation Option 1 for herbal preparations but are significantly different to Consultation Option 2 for lead. Both are not considered for dose, as are the ICH and USP international standards. By applying concentration limits for the finished product, neither option causes the same outcomes as the recent international benchmarks set by ICH (for non-herbal products) and USP (for herbals and non-herbal products). The TGO must not partially apply or use the documents with a different approach and intent. In particular Option 2 for herbal products is overly restrictive and therefore significantly increasing burden without need. To divert from internationally harmonised approaches is not supportable.

For herbal preparations and arsenic, we also note that the limits proposed in TGO 101 that appear to be the subset of ICH requirements which are not designed for herbal products, and it would not appropriately differentiate some materials. This alone would significantly increase testing costs without met value. The USP <2232> appropriately applies the limit to inorganic forms.

Adopting the USP <2232> in its entirety for all listed and complementary medicines (herbal and non-herbal), has been noted by our members as the only appropriate harmonisation proposal, preferably with the "equal but alternative" of the ICH requirements for Class 1 contaminants. Critical to this approach is access to and guidance regarding all available implementation options,

Recommendations – Elemental Impurities

1. **Primary recommendation**. The only acceptable internationally harmonised option for complementary medicines without an individual monograph, particularly herbal products, is the adoption of USP <2232> in its entirety.
2. **Secondary recommendation**. In addition to the above primary recommendation, it is highly desirable to have the ICH document for Class 1 impurities (with all available compliance options) adopted as an alternative, but equally available option to allow suitable flexibility

for different products including for manufacturers with trade requirements for different countries.

3. **Transition**. As a new and increased regulatory requirement, it is absolutely necessary to have a minimum transition period of three years to ensure that all manufacturers can work through supply chains for raw materials and set new procedures in place. It also allows laboratories to make the necessary infrastructural changes to meet a change in demand.
4. **Impact assessment**. We note that any increase in regulation requires a degree of regulatory burden assessment, however it is our view that any approach other than that described above, for listed complementary and herbal medicines, would require a full Regulatory Impact Statement.
5. **Implementation & guidance**. TGA guidance must include risk assessment forms to assist manufacturers apply limits through to finished products, against the various possible compliance options in the USP and ICH, to assist achieve compliance expectations and a simplified reduced burden approach.

Dissolution (modified-release tablet or capsule)

Modified release multiple active products

The TGO 101 does not contain any exemption for multi-active tablets or capsules, for which it is generally not technically feasible or necessary to conduct a dissolution test for each active. The assay of multi ingredient tablets and capsules is difficult when specialised extraction and concentration methods are applied. Multiple active products often require several different solvent extraction and HPLC or other assay systems to achieve reliable assay outcomes that avoid interferences from other ingredients, particularly herbal ingredients or excipients. To conduct dissolution testing, a single extraction (dissolution) in a buffer medium would be unlikely to allow accurate quantitation of any or all of the multiple active ingredients.

Item 18 (2) in the draft TGO 101, that relates to modified release tablets or capsules, is similar to 10 (c) in TGO 78, in that it does not describe what is or should be conducted in practice for listed

medicines. Disintegration testing for enteric coated /modified release tablets or capsules would be performed as per the pharmacopeia. It is normal practice for sustained (enteric coated) or modified release tablets or capsules to be subjected to a disintegration test, involving disintegration media at different pH levels, to demonstrate that enteric coated tablets or capsules do not rupture at low pH levels consistent with gastric contents, but rupture within an appropriate time period when subjected to higher pH levels consistent with intestinal contents. It is also not technically feasible to monitor dissolution of each active ingredient in multi-ingredient tablets or capsules, whether sustained release or not.

Soft gel capsules are designed to immediately release once the shell is broken, so it would be expected that dissolution is essentially immediate. When enteric-coated softgel capsules rupture, the contents are released immediately, making it no more necessary to conduct a dissolution test than for an uncoated softgel capsule. For materials such as colecalciferol, these materials are encapsulated as stabilised formula, and at the low concentrations, they would be extremely difficult if not impossible to assay for in the dissolution buffer medium. Where other oil based products (peppermint, fish, krill, evening primrose oil etc) are concerned, these oil based capsule fills would be poorly soluble in traditional dissolution (aqueous buffer) medium and not reflect absorption or bioavailability. Additionally, methods used to assay for these materials would not be adaptable to dissolution medium based extraction.

Recommendations – Dissolution, Disintegration for modified release dosage forms

1. Section 18 must be amended to exclude the requirement for dissolution testing (other than for folic acid) for multi-active tablets or capsules.
2. Subsection 18 (2) be removed from the section headed “Dissolution” and placed in a separate section headed “Sustained or modified release tablets or capsules”, which describes appropriate (pH modified) disintegration tests that should be applied to such products.

Residual solvents

Ph.Eur. 5.4 proposed for all listed and registered medicines is not applicable to listable medicines, as per the preface statement. CMA members have widely commented that the only residual solvent generally associated with complementary medicine manufacture is ethanol, which is widely used and indispensable in medicine manufacturing for granulation and coating steps. Ethanol is a Class 3 solvent, where a limit of "not more than 0.5%" is applied by Ph.Eur 5.4. Complementary medicine manufacturers are concerned about having to test listed medicines for residual ethanol without due purpose. Its risk profile to the end consumer is extremely low, even if present at the maximum 0.5% of the product – for example, this is equivalent to or less than the amount permitted in beverages such as fermented non-alcoholic beverages that deliver a far high quantity by volume.

Members have found in practice that even at a level of 0.5% ethanol can be detected using olfactory methods, which are routinely used during in-process checks. While the monograph allows the use of Loss on Drying as a suitable testing method, this is not as simple as it seems, as it does not take into account natural moisture content in the product. If industry were required to invest in Headspace Gas Chromatography instrumentation to determine residual ethanol, this would be a very significant cost impact to industry and consumers offering little to no risk-commensurate value, including ongoing reagent and personnel costs and similarly to the need to potentially purchase ICP-OES or ICP-MS instrumentation to test elemental impurities, and require a regulatory impact statement.

CMA members have also noted that recently-revised guidance documents published on the TGA website and produced by the GMP area do not include requirements for residual solvent testing and question why such requirements are specifically being proposed for discrete oral dosage forms.

Recommendations – Residual Solvents

1. Residual solvent Ph.Eur 5.4 is not included as an Australian specific requirement – as per international standardisation, it should only be required where pharmacopoeial monographs for tablets and capsules specify it.
2. If considered necessary, separate guidance could be provided describing a risk management approach for Class 3 solvents such as ethanol.

Alternative standards with additional requirements.

CMA notes that this document represents a significant change in approach to standards for finished products, by employing a system of alternative available standards, which we do not oppose, but that also cross-references additional standards. Alternative standards are intended to reduce burden, but in practice it is confusing and additional red-tape to include a complex list of cross-referenced additional requirements. While it may be necessary under limited circumstances, such as folic acid dissolution, it is undesirable to start a complex system of taping together different requirements unless critical, and thought-out from all technical perspectives.

The alternative standards approach is a new approach may raise practical challenges in implementation that are not currently apparent; future amendments to the TGO may be needed.

Recommendation – Alternative Standards

1. The concept of alternative standards is supported, however the addition of new cross-referenced requirements to existing pharmacopoeial standards is a deviation from international approaches, creates red-tape, and must be minimised unless widely accepted as necessary for health and safety. If challenges arise, further consultation may be required.

Other requirements currently not flagged for change

There are many requirements are not changing from the existing TGO 78. Unless specifically noted in this submission, CMA supports carry-over of existing requirements.

There have been some examples of recent consultations, with new and additional restrictive changes introduced at a late stage without adequate consultation despite the level of impact for varying stakeholders they can represent. We are concerned about this development in regulatory approach and wish to avoid this occurring for this document, unless any changes have been specifically supported. We would prefer to view the final draft TGO before implementation.

Recommendation – requirements not currently flagged for change

1. Any changes that may occur after the consultation period, but before publication and that have not been consulted or agreed upon, must have further consultation and assessment.

Proposed Guidance

As noted above, we believe that the guidance must include increased information and risk assessment forms to assist manufacturers of all sizes to comply with the USP <2232> (and ICH as possible second equal but alternative option), relevant to all the options available in the documents. Simplified options for compliance are preferred to ensure compliance and thereby helping to meet consumer outcomes but reducing possibility for misinterpretation and regulatory resource burdens.

We note that the guidance document includes a large amount of information on best practice for dosage form such as size of dosage form, shape and physical attributes (FDA), but submit that this is not the best place or this particular guidance, as TGO 101 does not include them as requirements.

Conclusion

CMA appreciates TGA consideration of the technical details and overarching Governmental policy considerations outlined within our submission. Our recommendations have proposed equivalent, sensible requirements that align with standard feasible practices and/or international documents prepared by expert committees.

A review of the final draft is preferred and has proven its value in prior consultations. We are willing to discuss matters at any time, and specifically request this if new or additional requirements that are not currently expressly supported are drafted. We appreciate your time in understanding the views put forth in this submission and look forward to continued collaboration on the requirements. If there are any items that require clarification, please do not hesitate to contact us.

Recommendations Summary

Recommendation – Scope

1. Reconsideration of applying TGO 101 to all discrete oral solid dosage units, including soft pastilles or gummies, or a description of relevant arrangements that allow for appropriate harmonisation.

Recommendations – Elemental Impurities

1. **Primary recommendation**. The only acceptable internationally harmonised option for complementary medicines without an individual monograph, particularly herbal products, is the adoption of United States Pharmacopoeia Chapter <2232> in its entirety.
2. **Secondary recommendation**. In addition to the above, it is highly desirable to have the ICH document for Class 1 impurities (with all available compliance options) adopted as an alternative, but equally available option to allow suitable flexibility for different types of products including for those manufacturers with trade requirements for different countries.
3. **Transition**. As a new and increased regulatory requirement, it is absolutely necessary to have a minimum transition period of three years to ensure that all manufacturers can work through supply chains for raw materials and set new procedures in place. It also allows laboratories to make the necessary infrastructural changes to meet a change in demand.
4. **Impact assessment**. We note that any increase in regulation requires a degree of regulatory burden assessment, however it is our view that any approach other than that described above for listed complementary and herbal medicines would require a full Regulatory Impact Statement.
5. **Implementation & guidance**. The TGA's guidance must include risk assessment forms to assist manufacturers apply raw material limits through to finished products against the various possible compliance options in the USP and ICH, in accordance with assisting compliance and providing a simplified approach.

Recommendations – Dissolution, Disintegration for modified release dosage forms

1. Section 18 must be amended to exclude the requirement for dissolution testing (other than for folic acid) for multi-active tablets or capsules.
2. Subsection 18 (2) be removed from the section headed “Dissolution” and placed in a separate section headed “Sustained or modified release tablets or capsules”, which describes appropriate (pH modified) disintegration tests that should be applied to such products.

Recommendation – Residual Solvents

1. Residual solvent Ph.Eur 5.4 is not included as an Australian specific requirement – as per international standardisation, it should only be required where pharmacopoeial monographs for tablets and capsules specify it.

Recommendation – Alternative Standards

1. The concept of alternative standards is supported, however the addition of new cross-referenced requirements to existing pharmacopoeial standards is a deviation from international approaches, creates red-tape, and must be minimised unless widely accepted as necessary for health and safety. If challenges arise, further consultation may be required.

Recommendation – requirements not currently flagged for change

1. Any changes that may occur after the consultation period, but before publication and that have not been consulted or agreed upon, must have further consultation and/or impact assessment.