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Dear [redacted]

ASMI Response - **Consultation: Remaking Therapeutic Goods Order No. 78**

ASMI welcome the opportunity to respond to this consultation. The ASMI secretariat have been very concerned at the limited member response to this highly technical consultation. This is not due to lack of interest or a sense that there is no impact on their products. It has been driven due to timing of the consultation over Australia's long summer holiday period, coupled with the overwhelming workload in implementing other reforms: TGO 92, permitted indications, review of all advertising to the new TGAC on top of business as usual. Members have been apologising for not having the resource capacity to deal with this. As such only a few members have been able to assist the secretariat with comment. TGA should be aware of the potential impact on the quality of the consultation.

This is important background for TGA to understand generally, that while the majority of the MMDR has now been put into effect in legislation and the project is complete from the TGA's perspective, the industry needs a period of space and stability to implement and comply with the plethora of reforms, layers upon layers of changes with differing transition periods that have been introduced to their products over the last 2-3 years.

Key messages from our response are:

- The overall approach to the introduction of the default standards and establishing an Australian specific minimum standard is a good concept.
- The Order and the Guidance have been well drafted, particularly given the timeframe available.
- There are what we consider to be some unintended drafting errors identified in both documents and further guidance might be provided in some areas. Additionally we suggest that the provision of educational sessions may be beneficial to support the implementation of the elemental impurities requirements. The GMP Forum may provide a timely and appropriate vehicle for these sessions.
- The regulatory burden has been misunderstood and therefore underestimated, primarily due to the introduction of harmonised elemental impurities and the revised requirements for dissolution for registered tablets and capsules.

- We recommend that a 2 year transition period will be necessary for sponsors to comply with the new requirements and that TGO 78 will need to be remade without amendment to facilitate the transition.
- The consultation expectation to choose between Option 1 (BP) and Option 2 (USP) for elemental impurities limits for herbal materials or herbal preparations doesn't provide for harmonisation. In the absence of either established Permitted Daily Exposure (PDE) within the Australian environmental context, or an understanding of risk assessment outcomes of existing products, sponsors have no reference for an informed decision. We therefore suggest a combination of Option 1 and 2 would be more suitable i.e. adopting the limits of Option 1 for the majority of elements, however including the mercury limit as per Option 2.

ASMI remain committed to supporting the implementation of an effective and efficient replacement Order for TGO 78. We are keen to participate in further consultative forums to assist in this process. We hope that our response is constructive to this end. Should you require any further clarification please don't hesitate to contact us.

Yours faithfully

About ASMI

ASMI (Australian Self Medication Industry) is the peak body representing companies involved in the manufacture and distribution of consumer health care therapeutic goods (non-prescription over-the-counter and complementary medicines including vitamins, minerals and supplements) in Australia. ASMI also represents related businesses providing support services to manufacturers, including advertising, public relations, legal, statistical and regulatory consultants. More information about ASMI and our membership is available on our website.

The purpose, scope and background of the consultation

ASMI appreciate and support the need for the update to TGO 78 to:

- Introduce the application of default standards (ASMI supports the overall approach taken for the introduction of the default standards and establishing an Australian specific minimum standard.
- Reflect updates to international standards.
- Provide for greater levels of harmonisation and clarity of requirements
- Reintroduce the chemical and physical testing of pills

Imminent sunsetting of TGO 78 and need for transition

TGO 78 is due to sunset on 1 April 2019. The initial TGA consultation with industry stakeholders conducted in accordance with the *Sunsetting legislative instrument guidance note*, to confirm the order was operating 'effectively and efficiently', was presented in terms that the order would be remade without amendment and once remade a thorough consultation would commence to ensure that there was sufficient time to consider the needs of an order to replace TGO 78 with a revised order that was fit for purpose and aligned internationally where appropriate.

However the plan has changed to attempt to replace TGO 78 prior to the sunset date and now ASMI (and TGA) are now rushed into developing a new order, with consultation over the long summer holiday period, while key staff of member companies are on leave or are inundated trying to implement and comply with the multitude of MMDR reforms effecting all facets of processes that impact the supply of product. On 4th December ASMI raised our concerns at this revised approach, warning that ultimately both TGA and Industry will need to work with the new order over its 10 year life span and therefore the importance of taking the time to consult on producing an effective order.

Despite the proposed Guidance for TGO 101 indicating the allowance of a transition period of a year –until 31 March 2020, to comply with TGO 101, ASMI have interpreted the absence of a transition period in the draft TGO 101, backed by the repeated assertions in the consultation paper that no transition will be necessary as the TGA's proposal for implementation. The absence of transition is not acceptable.

For our members the most concerning aspect of the consultation is the statement that:

> *"The remade Order* [TGO 101] *will allow sponsors to maintain compliance with existing requirements. Alternatively, they may choose to align with internationally-harmonised requirements as permitted in the Order at any stage. This means that a transition period is not required."*

The proposed TGO 101 does however introduce significant new requirements for products which will leave sponsors/manufacturers of both listed and registered tablet and capsule products non-compliant with the Order when it is introduced on 1 April 2019 and therefore non-compliant with their obligations under the Act.

The scope of the work necessary to confirm/achieve compliance cannot be carried out within the timeframe leading up to the effective date and in any event there would be a lack of clarity of the final requirements of the Order until it is published. Based on all the necessary steps it is estimated that 2 years would be necessary to complete the scope of works to ensure sponsors' products can be manufactured compliant with the Order.

TGO 101 introduces two specific requirement areas which generate the need for a transition period:

- the first is the revised expression of the dissolution requirements for registered tablets and capsules under sections 12 and 18. This may be an inadvertent/unintended drafting error, however we can only interpret the Order as written.
- the second is with respect to the adoption of internationally-harmonised limits for impurities. The consultation paper acknowledges that these were recently introduced into the BP (1 January 2018). So while not technically 'new' for registered and listed *tablets or capsules with an individual British Pharmacopoeia monograph* under TGO 78, it does represent a new requirement for those registered and listed *tablets and capsules without an individual British Pharmacopoeia monograph* under TGO 78 – referred to in this consultation as 'Australian specific requirements'.

More detail on the assessment of regulatory burden of these changes and the importance of a period of transition is presented under Implementation and Transition from TGO 78 to TGO 101

In this light, ASMI's preferred outcome of this consultation is to remake TGO 78 and once remade revisit this approach to TGO 101 when the TGA and the industry have had sufficient time to confirm the Order will be fit for purpose.

Where the outcome of the consultation is to push on to replace TGO 78 with TGO 101, we estimate that a 2 year period will be required to confirm and achieve compliance with the new requirements. We believe that the most comprehensive approach to allowing for transition is to remake TGO 78 without amendment for the period of that transition.

Review of each of the proposed changes to the Order

Recognition of default standards in the *Therapeutic Goods Act 1989*

ASMI is supportive of the inclusion of default standards in TGO 101, and the provision of a level of choice of international standard to achieve compliance. However the principles of harmonisation are diluted each time additional requirements are specified or limits are changed, rendering the requirements uniquely Australian.

We welcome the inclusion in the Guidance for TGO 101 of the additional explanation of *Applicable monographs* as an important clarification.

It may be necessary for the Guidance for TGO 101 to provide more detail on how to appropriately apply the specific monographs for dietary supplements in the USP – in particular where there might be more than one monograph that could be applied to a product. Additionally guidance on the acceptability and/or interpretation of the terminology *'other substances generally recognized as safe, in amounts that are unobjectionable'* within the Australian regulatory framework may provide greater confidence for application of the USP NF specific monographs.

Adoption of internationally-harmonised limits for impurities

The consultation paper acknowledges that the harmonised limits for impurities were recently introduced into the BP (1 January 2018) and that while not technically 'new' for registered and listed *tablets or*

capsules with an individual British Pharmacopoeia monograph under TGO 78, it does represent a new requirement for those registered and listed *tablets and capsules without an individual British Pharmacopoeia monograph* under TGO 78 – referred to in this consultation as 'Australian specific requirements'.

The ICH Q3D internationally has been implemented in stages as it is a completely different approach to the control of impurities based on quality risk management. In August 2015 ASMI submitted comment with respect to the proposed adoption of the Quality Guideline - CHMP/ICH/353369/2013 ICH Q3D Impurities: guideline on elemental impurities. Our request for exemption for application to Complementary and OTC Medicines was granted by way of the following annotation:

> *This guideline applies to registration applications for prescription medicines.*
> *The date for coming into effect in Australia aligns with implementation in the EU(link is external): From June 2016 for new products containing new drug substance/s; from December 2017 for new products containing existing drug substance/s.*

This annotation has since been removed without advice and without being archived. The enormity of the requirement is clearly demonstrated in the annotation limiting application to new prescription medicine and staged for NCEs and a more than a 2 year timeframe for applications for new products containing existing drug substances to comply. Our industry sector had therefore not been anticipating the plans for harmonised adoption of the requirements of ICH Q3D for elemental impurities into the EP/BP and USP pharmacopoeias and the removal of heavy metal limits from the drug substance and excipient monographs and therefore the retrospective application to all existing products from January 2018.

Therefore unlike the majority of updates to the BP/EP/USP, where a number of new or amended monographs are introduced and a few products in a Sponsor's portfolio of products may require updating, this update has introduced wholesale change across all products. Adopting this requirement into the TGO 101 without a transition period is extremely problematic.

Larger member companies who have worked as part of a global team project on implementing the ICH Q3D across their product portfolio have advised the extent of the work involved. Some have advised that after more than a year they have not yet finalised their risk assessments for all products but for those where they are still to obtain all necessary data from suppliers, they advise a level of confidence of compliance has been established.

With the Therapeutic Goods Order taking precedence over the Default Standards and with the majority of listed tablets and capsules complying with the Australian specific requirements, these requirements are new to the Australian industry. For the majority of listed and registered complementary medicines the signal of the need to start risk assessments to these new limits will have only now been received with the release of this consultation. (Although maybe not because it was not flagged.)

Some divergence has occurred during introduction of the limits for heavy metals into the BP/EP/USP:

- Where the BP has introduced limits to the General Monographs and removed the heavy metal tests from the specific substance monographs, the USP has gone a step further and has also removed the heavy metals test method. The latter is concerning should sponsors still wish to maintain this testing as a mechanism for control.
- The BP and the USP have used different approaches to determine acceptable elemental impurity levels with a considerable discrepancy between the BP Herbal Drugs monograph and the USP ⟨2232⟩ Elemental Contaminants in Dietary Supplements monograph.

In TGO 101 the use of the broad terminology 'Impurities', which could include residual solvents, sulfated ash, heavy metals and related substances (synthetic impurities and degradants) is somewhat confusing, particularly with respect to sections 11 and 17 which appear to only determine specific requirements to heavy metals (and residual solvents) in circumstances where no limit is otherwise applied. The general monographs of the BP and USP use more specific terms 'elemental impurities' and 'elemental

contaminants' respectively. The Guidance for TGO 101 provides background to impurities, elemental impurities, heavy metals and the introduction of consistency and clarity of limits for residual solvents and heavy metals. We question if the terminology in the Order should be consistent with the default standard terminology for example 'Elemental impurities and residual solvents' or if the intent of the broader term 'Impurities' in the heading requires greater explanation within the guidance.

Testing of elemental impurities in the finished product is not required if the risk-assessment concludes that no additional controls are required at this level, however this is only articulated in the guidance and should be more clearly expressed in the Order. The Guidance for TGO 101 states:

> *Sponsors and manufacturers may be able to justify the absence of an impurity test in finished goods specifications or the use of reduced or rotational testing.*

If not articulated in the Order, the minimum quality standard for tablets, capsules and pills, a specification for elemental impurities would be assumed to be reflected as a minimum standard in the finished product specification. This would mandate unnecessary work for sponsors to update their finished product specification, and would be particularly frustrating for those who have already conducted their risk assessments of elemental impurities. However the intent of ICH Q3D is not to simply transfer the control of elemental impurities from testing specifications for starting materials (as required by pharmacopoeial specific monographs) to establishing specifications for testing of the finished product. Rather, ICH Q3D provides for a quality risk management approach specific to the product, to assess and understand the potential sources of elemental impurities, to determine and control the total elemental impurity level relative to the PDE. Where elemental impurity levels exceed the threshold, the necessary measures must be implemented to achieve and maintain control at the source(s). Within the risk assessment this is an iterative process. Typically starting material specifications may need to be updated. As indicated in the Guidance for TGO 101 the implementation of such controls at the finished product specification would be a measure of last resort, where routine or periodic confirmation of control would be required.

Impurity limits for herbal preparations

The consultation paper asks the industry to select between Option 1 - based on the BP Herbal Drugs monograph limits for arsenic, cadmium, lead and mercury and Option 2 - based on the USP <2232> Elemental Contaminants in dietary supplements limits for arsenic, cadmium, lead, total mercury and methyl mercury. It is questioned why the additional test for methyl mercury is necessary.

It is not clear why Option 1 has substantially lower limits for mercury, and what the relevance of this is to the Australian environment and population, similarly Option 2 has far lower limits for lead. Essentially, BP and USP have reached vastly different parameters based on their physical and regulatory environments and it is likely that further consideration should be given to how PDEs should be translated into dosage limits specific to the Australian context.

Members advise that it is impossible to make an informed proposal in the absence of the risk assessments on affected products. Regardless of which option is chosen, in effect the products imported from regions complying with the alternative option will be subjected to a new 'Australian specific requirement'.

Consideration should be given as to whether a combination of Option 1 and 2 would be more suitable i.e. adopting the limits of Option 1 for the majority of elements, however including the mercury limits as per Option 2 but excluding the USP additional test for methyl mercury to avoid creating an Australian specific requirement.

Both options for limits for elemental impurities in herbal preparations present significantly tighter limits than have been conventionally applied. The introduction of either of these options is likely to present very real business impacts on supply chain and formulations in order to maintain compliance.

Section 17 (c) restricts application of Schedule 1 item 3 to tablets or capsules containing one or more actives, "each of which are herbal materials or herbal preparations''. This means that all tablet and capsule products containing non-herbal complementary medicine actives or those actives in combination with a herbal active must comply with the ICH limits listed in Schedule 1 item 2. Again while it is hard to predict, this is likely to be overly restrictive for the Australian market, relative to the rest of the world.

Residual Solvents

Sponsors/manufacturers of non-prescription medicines have typically only tested for residual solvents in finished product where it is included in the registered finished product specifications. Therefore similar to the introduction of elemental impurity limits, the residual solvents limits will represent an additional uncertainty for product compliance. It will require sponsors to conduct a risk assessment and introduce an additional testing requirement for finished products unless the risk assessment provides justification that it is unnecessary.

ASMI suggest that the draft TGO 101 requires greater clarity around requirements for residual solvents. Both Sections 11 and 18 make no mention of residual solvents. While Section 18 (b) & (c) refer to Schedule 1 items 2 & 3 respectively and the requirement for residual solvents is specified, we question if in the drafting of Section 11 reference to the requirements for residual solvents may have been overlooked.

Dissolution requirements

The revised wording in TGO 101 for the requirements for dissolution used in both sections 12 and 18 of TGO 101 creates a change of requirement:

> *"a default standard in relation to any active ingredient contained in that tablet or capsule specifies a dissolution test; then that dissolution test is specified for the tablet or capsule."*

This implies industry could be forced to adopt inappropriate dissolution tests for some formulations. The dissolution requirements appear to introduce multiple standards that could be conflicting, particularly given the reference to the active ingredient – this suggests that a dissolution test could be required to be applied regardless of whether the dosage form or formulation is appropriate. A dissolution test for one active ingredient in a multi ingredient tablet or capsule may not be applicable for every active ingredient in that tablet or capsule so it should be limited to the active ingredient only. For example, could this wording mean having to apply the dissolution test from a specific monograph for actives in combination because that monograph includes one of the active in your product, regardless of what your product's combination of actives may be?"

If there are multiple active ingredients in a tablet with dissolution tests in several specific monographs there could end up being multiple different dissolution tests that need to be performed.

Typically, control of drug release (be it by dissolution or disintegration) is specified in the general chapters, and approved as part of the registration. Medicines approved prior to the development of a specific monograph may or may not meet the dissolution test in the monograph, but have still been assessed as including a suitable dissolution test, to demonstrate the release of the active substances.
Compliance with default standards should also be sufficient for tablets and capsules, similar to other dosage forms. The TGA should not impose additional requirements for products beyond the applicable monograph the sponsor has chosen to follow. The additional TGA specific requirements create unnecessary burden for sponsors who market products in other jurisdictions where there are no additional requirements.

This change to dissolution requirements will require sponsors of all registered tablets and capsules, whether currently complying *with an individual BP monograph* or with the Australian specific requirements

to reassess the basis of their current dissolution test method and specification. They will need to either confirm that there are no specific tests identified in a default standard for any of the active ingredients in the product or where any test does exist, that test will need to be applied.

The TGA should retain the reference to "a suitable test for dissolution" as per the current TGO 78 and the general monograph of the BP. This will ensure requirements for Australian tablets and capsules for dissolution remain appropriate and consistent with the approach of the rest of the world.
The current TGO 78 wording aligns with the wording in the current BP General Monograph for Tablets - test for dissolution – *'A suitable test may be carried out to demonstrate the appropriate release of the active substance(s), for example one of the tests described in the general chapter 2.9.3 Dissolution test for solid dosage forms.'*

If the wording of the proposal for dissolution requirements is intended, it is introduced at a time when the European Pharmacopoeia have released a consultation recognising some of the problems in the way dissolution is currently addressed in the pharmacopoeia. It recognises the importance that the dissolution method is suitable for the product's actives, dose form, formulation and method of manufacture. The consultation is titled *Dissolution test in individual monographs on solid oral dosage forms: Your feedback counts!* It is a survey of medicine authorisation holders and other stakeholders presenting two options:

- Option 1 is to allow for a different dissolution method and/or acceptance criterion than in the monograph,
- Option 2 is to no longer specify a dissolution test method at all in the individual finished product monographs but to mandate the requirement for a suitable dissolution test method.

From a transition perspective, ASMI would also like to understand the implications for a Sponsor who has an existing in-house/suitable test for dissolution that has been demonstrated to be equivalent to the pharmacopoeial method and approved by TGA. Would this method now be superseded by the TGO 101 requiring a change to the method. With the number of products reviewed and approved under the TGO 78 option of 'a suitable test for dissolution', ASMI again recommend this current allowance and wording of the Order be retained to ensure the regulatory burden is minimised.

The dissolution requirements for the dose forms listed in Section 12 (a) (ii) are left ambiguous (i.e. modified release tablet, chewable tablet, effervescent tablet, dispersible tablet or modified release capsule). We question if there been an omission of a requirement similar to that included under Section 18 (2)- *If the tablet or capsule is a modified-release tablet or capsule, then a test for dissolution that demonstrates the appropriate release of each active ingredient must be performed.*

In Division 3, section 18 the dissolution requirements need to be revised to include that for a registered multi-active ingredient formulation (e.g. registered complementary medicines) it is suitable to comply with the dissolution requirements of USP NF <2040>, as per current TGO 78.

Widening stated content limits within the Order

ASMI supports the application of the proposed Schedule 2 content limits within the order to both listed and registered goods. This addresses issues experienced particularly with registered multivitamin and mineral products. It recognises that the substances are not rendered with a greater level of stability due to their inclusion in a registered finished product.
We do however hold concerns that the schedule has not considered any newer naturally derived listed substances for the need for wider limits since TGO 56. A range of substances used in listed medicines are not captured within Schedule 2 (e.g. herbal materials, naturally derived substances) that will generally comply with the listed 90-120% limit, however the ongoing requirement to apply and maintain consent notices for non-compliance with the registered limits of 90 – 110% create a barrier for use in registered complementary medicines.

Applications for exemptions from compliance with TGO 78 have been required for both listed and registered products for some naturally derived substances beyond the 120% limit. Over the life of TGO 78 the TGA policy for granting exemptions to a standard has changed from allowing for 'enduring' exemptions, to only being allowed for time limited periods or batch specific cases. The enduring consent (i.e. for the life of the Order), considered; the risk to the patient, reflected the characteristics of the ingredient, the level of the sponsor's influence to change/improve compliance. Time limited exemptions are generally granted for no more than 2 years. This type of period does not provide for commercial certainty for investment in launching the product, with the risk that a subsequent exemption application may be rejected.

As part of due process for implementing TGO 101 under the terms of the current consultation i.e. with no transition, the TGA has already issued notices to all sponsors who hold current exemptions granted with respect to TGO 78, advising that applications must be made for a new consent notice if the goods are unable to meet the requirements in the remade Order.

We therefore propose the following additions to the current proposed Schedule 2 for practical resolution of the ongoing management of the issues related to these substances.

Additional substances for consideration: Schedule 2

Active ingredient	Not Less Than (per cent)	Not More Than (per cent)	Comments and/or justifications
Carotenoids e.g. lycopene, lutein, zeaxanthin, astaxanthin	90.0	165.0	Betacarotene (carotenoid included in Schedule 2) has a range of 90-175% - similar characteristics for other carotenoids, with demonstrated stability challenges. Lycopene – Previous S14 exemptions including 90-165% and 90-140%. Lutein – Previous S14 exemptions including 90-135% and 90 – 165% and 90 – 150%, Astaxanthin – similar structure, no monograph. Zeaxanthin – similar structure, no monograph.
Medium-chain fatty acids/triglycerides e.g. octanoic acid, myristoleic acid	90.0	(?)	Suggested for inclusion due to stability characteristics. Justification and upper limit to be developed
Long-chain fatty acids e.g. docosahexaenoic acid, eicosapentanoic acid, alpha-linolenic acid	90.0	(?)	Suggested for inclusion due to stability characteristics. Justification and upper limit to be developed
Mono & polysaccharides e.g. glucosamine, chondroitin	90.0	120.0	Justification to be developed. Inconsistency in the allowable limit for listed complementary medicines (90 - 120%) and registered complementary medicines (90 – 110%).
Organosulfur compounds e.g. glutathione, lipoic acid, cysteine, taurine, s-adenosylmethionine, indoles	90.0	120.0	Justification to be developed. Inconsistency in the allowable between limit for listed complementary medicines (90 - 120%) and registered complementary medicines (90 – 110%). R,S-alpha lipoic acid – Previous time limited S14 exemption (90 – 130%)
Sugar alcohols e.g. inositol	90.0	150.0	Justification to be developed

Active ingredient	Not Less Than (per cent)	Not More Than (per cent)	Comments and/or justifications
Amino acid materials L-Carnitine, pyruvates, dimethylglycine hydrochloride	90.0	120.0	Assorted substances for consideration. Justification to be developed

ASMI request clarification with respect to 'Not less than stated content' in relation to log variability for Probiotics as included in Schedule 2 item 4 either as a footnote or provided the Guidance for TGO 101. The uncertainty over how to understand error for live organisms has been an ongoing issue between manufacturers and sponsors. Consider allowing +/- 0.3 - 0.5 log variability from label claim for the assay specification for the permitted count.

Reintroduction of pills to the scope of the Order

ASMI supports the reintroduction of pills to the scope of the Order.

With the approach of reproducing the chemical and physical test requirements from the Chinese Pharmacopoeia, we suggest a process for consideration of future amendments to the pharmacopoeia and how these changes will be adopted, may be appropriate to ensure the ongoing management of this Order and to maintain harmonisation.

Medicines that are not subject to the Order

ASMI supports the increased clarity around the scope of the Order in relation to unapproved goods.

- Goods not required to be on the ARTG
- Exempt medicines

The treatment of **other discrete dosage forms** such as soft lozenges and pastilles raises some inconsistencies of approach.

From the perspective of:

- registered medicines - it can be questioned why compliance with a default standard without additional Australian specific requirements cannot similarly and simply be applied to Tablets and Capsules. The imposition of additional requirements where a sponsor has chosen to follow a particular applicable monograph can create unnecessary burden for sponsors.
- listed medicines - it can be questioned why allowances provided for listed tablets and capsules should not equally apply to other discrete dosage forms.

Other changes introduced in the draft TGO 101

ASMI question other changes that have been introduced to TGO 101 which were not anticipated:

- Disintegration,
  TGO 78 section 10 (d) requires *the relevant test for disintegration (if any) of the British Pharmacopoeia, in the general monographs "Tablets" or "Capsules", respectively;* where the proposed TGO 101 states compliance in accordance with Schedule 1 item 4 – which describes only the test of USP/EP. To avoid confusion, the relevant tests of all the default standards BP/USP/EP should be listed. While this may seem a minor matter – it may require companies to update

existing test methods and finished product specifications to reflect the mandated requirements of the Order.

The revised wording of Sections 18 and 19 now reads to mandate disintegration testing of chewable tablets and needs to be corrected. Chewable tablets are formulated to be disintegrated by chewing. The default standards do not mandate disintegration tests on chewable tablets. If not corrected this will introduce a new and unnecessary test for all registered and listed chewable tablets.

- Uniformity of dosage units and uniformity of weight (mass)
  Similar to the entry for disintegration, Schedule 1 items 5 and 6 – describe only the tests of the USP/EP. To avoid confusion, the relevant tests of all the default standards BP/USP/EP should be listed. Similarly – this can generate regulatory burden for sponsors/manufacturers in updating existing test methods and finished product specifications to reflect the mandated requirements of the Order.

  Additionally ASMI request that Listed goods be able to choose whether to apply item 5 (uniformity of dosage units) or item 6 (uniformity of mass) in Schedule 1. This is consistent with section 13 that gives the option of using uniformity of mass. Sponsors should not have to apply for an exemption if they choose to use uniformity of dosage units.

Implementation and Transition from TGO 78 to TGO 101

ASMI members are clear that:

1. A transition period will be critical for the non-prescription medicine industry to achieve compliance with the new requirements in TGO 101; and
2. TGO 78 will need to be remade for a period to provide for a suitable transition mechanism.

On 22 November, prior to the release of this current consultation, we wrote to you expressing our concerns that the TGA's proposed approach, at that time, as now, was not seeking to remake TGO 78 to provide for a period where both TGO 78 and TGO 101 are in effect - in recognition that there is significant work that will need to be done to *confirm* and in some cases *achieve* compliance with TGO 101. (In a similar way to the transition provided between TGO 69 and TGOs 91 & 92).

When TGO 56 was superseded by the introduction of TGO 78 on 29th October 2008, a 2 year transition period was provided to update and validate analytical test methods and specifications for tablet and capsule products and vary ARTG entries accordingly. During this period each medicine had to comply with either TGO 78 or TGO 56. On and from 1 November 2010 compliance with TG0 78 was mandatory.

After reviewing the consultation documents and receiving feedback from members we now confirm that there are significant changes introduced to the Order for which a similar suitable transition period will be necessary.

While the consultation paper and guideline represent the extent of regulatory burden as 'low' and therefore no transition period is necessary, this does not reflect the true situation to confirm and achieve compliance with the standard. In focusing on quantifying the 'burden' of the change and how it can be minimised from a cost perspective, it overlooks the impact of the changes on the regulatory obligations for both the Sponsor and the Authorised Person (AP) for continued release of stock to the market.

For the AP to conduct Release for Supply of any tablet or capsule product they must confirm that the manufacture has been conducted compliant with the requirements of:

1. The Market Authorisation (ARTG entry).

2. All standards that apply to the product (TGOs) or written approval from the Secretary for not meeting that standard.
3. PIC/S Guide for GMP PE009-13

Therefore from 1 April 2019 without the provision of a suitable transition period from TGO 78 to TGO 101, Sponsors/manufacturers will be unable to confirm their products' compliance with the new elemental impurity limits or the new dissolution requirements. Without the evidence of confirmation of compliance with TGO 101 the AP is unable to meet their regulatory obligation and therefore cannot continue to release batches, until that information can be confirmed. When these 'minor changes/additions' are considered in this light, the regulatory burden becomes considerable.

Affected sponsors have already received advice that any consent notices issued for TGO 78 will no longer be in force once the instrument has sunsetted and that if those products are unable to meet the requirements in the remade Order, application for a new consent notice must be made. Application cannot be made until the remade Order is published and its detail assessed. Therefore no further batches of that product can be released from 1 April 2019 until a consent notice is issued and whether it will be issued is uncertain.

We therefore advise how critical it will be for the industry that a suitable period of transition is provided to meet these new requirements. We recommend that the most comprehensive mechanism to provide a transition is to remake TGO 78 without amendment for the period of transition so that sponsors/manufacturers can be compliant with either TGO 78 or TGO 101.

Assessment of Regulatory Burden

TGO 101 introduces two specific requirement areas which generate the need for a transition period:

- the first is the revised expression of the dissolution requirements for registered tablets and capsules under sections 12 and 18. This may be an inadvertent/unintended drafting error, however we can only interpret the Order as written.
- the second is with respect to elemental impurities limits.

1. Dissolution requirements for registered tablets and capsules

What this means is that sponsors will have to undertake the following tasks in relation to the dissolution testing for every one of their registered tablet and capsule products:

- Conduct a review of the current finished product specification/dissolution test methods against the requirements of the current BP and USP, in relation to any active in the product to assess if a specific dissolution test required is not being conducted, e.g. because it has previously been subsumed into a 'suitable test for dissolution'. For those products identified as requiring amendment to the dissolution test method and/or specification, work with the Manufacturer to commence:
    - Analytical method development and validation.
    - Revision the analytical method for dissolution
    - Revision the Finished Product Specification (FPS).
- Submit a variation to amend the registered details of the medicine,
    - if a new method can be developed and validated, or,
    - where a default standard specifies a test method for an active that is unsuitable and cannot be validated – apply for a S14 exemption justifying a suitable alternate.
- Notify the Manufacturer/Authorised Person once the variation/exemption is approved for commencement of the revised test method(s)/FPS.
- Provide the Authorised Person responsible for release for supply updated details of Market Authorisation (ARTG entry).

These steps (or steps to this effect) will need to have been conducted for all products assessed as impacted prior to the end of the transition date.

2. Introduction of elemental impurities limits and residual solvents

The consultation paper acknowledges that elemental impurity limits are additional requirements to the Australian specific requirements but advises their introduction:

> *"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."*

This provided example starts to identify the number of tasks a sponsor will need to undertake to confirm (or otherwise) each product's current compliance but does not reflect the time needed to generate new supporting documentation necessary to demonstrate compliance.

The process of conducting risk assessments for a broad range of products to understand elemental impurities in the context of the new narrower limits is not a simple task.The tasks involved for all tablet and capsule products to ensure compliance with the elemental impurities changes are as follows:

- Conduct a risk assessment on each product, this might include:
    - Sourcing and analysing data to establish the theoretical level of elemental impurities in the finished product contributed from starting materials and packaging and the manufacturing processes.
    - Determining the range of variability within anticipated from the sources.
    - As necessary, testing of finished product although this requires development of a suitable methods.
    - Confirming compliance with limits, where elemental impurity levels:
        - are below the control threshold, consider deletion of any existing general heavy metals tests from the starting material specifications.
        - exceed the control threshold, identify mechanisms to reduce levels at source, justify and implement necessary specific elemental impurities specifications determined by the risk assessment to starting materials and as necessary establish specification limits for elemental impurities in the finished product.
    - Documenting and maintaining the Risk Assessment.

- Where the level of the elemental impurities is determined to exceed the control threshold in the finished product, rather than attempt to impose new limits on starting material manufacturer, Australian sponsors are likely to need to commence a review of supply of those starting materials to ensure that finished product can be manufactured without risk of rejection. Tasks would include:
    - Establishing a change control for the product
    - Procuring actives and/or excipients or packaging from alternate sources.
    - Establishing new material specifications and supply and technical agreements.
    - Qualifying those sources of supply
    - Revising batch documentation
    - Validating the revised materials within the manufacturing process (including stability as required)
    - Submitting the necessary changes to the ARTG.
    - Advising the Manufacturer/Authorised Person responsible for release for supply of the date of effect of the new Order and updated Market Authorisation (ARTG entry).
    - Commence release of revised compliant product.

Unless a period of concurrent effect of TGO 78 is provided – there could be no certainty these products would be in compliance. Without an understanding of the range of variability of the levels of impurities

within the finished product, the introduction of finished product testing provides no certainty of compliance and represents a high level of commercial risk (batch failure).

Educational considerations

As the process of conducting risk assessments for a broad range of products to understand elemental impurities in the context of the new narrower limits is not a simple task, ASMI suggest that this transition may benefit from provision of education.

Many Australian Sponsors and Manufacturers particularly of lower risk products do not have the support of a global head office of specialist experts to advise and assist them. There may therefore be a high level of interest in education on how to approach the adoption of internationally-harmonised limits for elemental impurities. Accompanying guidance on possible allowable approaches like bracketing or grouping of products, may be helpful to support the local industry implement the change. It should be noted that application of quality risk management principles is 'relatively' recent requirement and the concept of lifecycle management is yet to be reflected in the PIC/S Guide. Therefore many Australian sponsors and manufacturers of lower risk medicines may still be working within older paradigms for product development and GMP.

The 2019 GMP Forum might be an opportunity for provision of practical seminars. ASMI would be prepared to support educational sessions with case study style practical presentations.

The Order – TGO 101

Please find a summary of comments to the draft TGO 101. [redacted]

- **Commencement:** ASMI advise that a 2 year transition period will be necessary for sponsors to comply with the new requirements and that TGO 78 will need to be remade without amendment to facilitate the transition.
- **Descriptions of application of Division 2 and Division 3:** require greater differentiation– i.e. more effective descriptions will assist understanding and navigation of the document. Suggested text is provided.
- **Making reference to another of the default standards:** We note that approaches to differ through the Order, with expressions regarding 'another standard' or 'another pharmacopoeia'. While default standards are clearly defined, this type of terminology used to reference from one default standard to another, has potential to be misinterpreted by users and to expand the scope of the Order beyond what is intended.
- It is unclear why the draft TGO 101 is at times selective of the default standards applied for example Schedule 1 items 4, 5 & 6 only makes reference to the EP and USP. It is unclear why the BP requirements for disintegration, uniformity of dosage units and uniformity of weight (mass) would be unsuitable. We recommend that where all default standards provide a suitable test, all (BP/EP/USP) should be listed.
- We note that the wording of Section 15 (2) currently allows for a much broader application of schedule 2 than we anticipate is intended.
- The term 'multi-component ingredient' is not defined and will require clarification for application in the Order.
- We question the requirement of Section 17 (c) which restricts application of Schedule 1 item 3 to tablets or capsules containing one or more actives, "each of which are herbal materials or herbal preparations". For consistency we raise the same issue for Section 29 (2).
- For Sections 11 and 17: The allowance that the Elemental impurities risk assessment process may allow sponsors and manufacturers to justify the absence of an impurity test in the finished goods specification MUST also be articulated in the Order. The Order represents the minimum quality standard, the inclusion of a specification for elemental impurities would otherwise be expected as a

minimum standard reflected in the finished product specification. It is therefore important to avoid mandating unnecessary finished product testing, that this allowance is provided in the Order. ASMI have proposed revised wording in Sections 11 and 17 of the Order.

- The revised wording in TGO 101 for the requirements for dissolution used in both sections 12 and 18 of TGO 101 creates a change of requirement: *"a default standard in relation to any active ingredient contained in that tablet or capsule specifies a dissolution test; then that dissolution test is specified for the tablet or capsule."* ASMI recommend that the TGA should retain the reference to "a suitable test for dissolution" as per the current TGO 78 and the general monograph of the BP.
- We question if the wording of Section 18 (2) allows for the selection of marker ingredients for establishing dissolution or will require 'each active ingredient' to be individually tested?
- We believe the drafting of Sections 18 and 19 have inadvertently introduced the mandatory requirement for disintegration testing of chewable tablets – imposing a requirement not required by the default standards BP/EP or USP.
- We question if Section 19 (2) should not only refer to section 18 but also to section 16.
- Under Section 21: we request the allowance that - Listed goods be able to choose whether to apply item 5 or item 6. This is consistent with section 13 that gives the option of using uniformity of mass. Sponsors should not have to apply for an exemption if they choose to use uniformity of dosage units.
- For Schedule 1 item 2 and item 3: we suggest changing the property name to 'Elemental impurities and residual solvents' rather than just 'impurities'.
- For Schedule 1 item: we propose an alternative harmonised option to the proposed Options 1 and Option 2.
- Schedule 1 items 4, 5 & 6 – describe only the test of USP/EP. To avoid confusion, the relevant tests of all the default standards BP/USP/EP should be listed. While this may seem a minor matter – it may require companies to update reference to their existing BP test methods and finished product specifications to reflect the mandated requirements of the Order. That is the need to generate unnecessary documentation updates to demonstrate compliance to the Order.
- Schedule 2: ASMI question if other ingredients of natural original require inclusion in this list – for example:
    - Listed & registered ingredients that have been subject to S14 exemptions requiring a limit >120%
    - Complementary medicine actives which if formulated for use in a registered medicine would currently be restricted to a maximum content limit of 110%. See ASMI proposed additions to Schedule 2 under the heading *Widening stated content limits within the Order*.
- ASMI request clarification with respect to 'Not less than stated content' in relation to log variability for Probiotics as included in Schedule 2 item 4 either as a footnote or provided the Guidance for TGO 101. The uncertainty over how to understand error for live organisms has been an ongoing issue between manufacturers and sponsors. Consider allowing +/- 0.3 - 0.5 log variability from label claim for the assay specification for the permitted count.

The Guidance for TGO 101

[redacted]

- Transition – reiteration of recommendation for 2 year period.
- Release v expiry specifications – suggested revised wording.
- The treatment of **other discrete dosage forms** such as soft lozenges and pastilles raises some inconsistencies of approach across solid dose products.

- Further guidance is required on applicable monographs where there are multiple USP-NF monographs which might apply. How should sponsors determine the most appropriate monograph for application to their product? See for example the number of specific monographs for calcium containing products.
- Additionally guidance on the acceptability and/or interpretation of the USP-NF phrase - *'other substances generally recognized as safe, in amounts that are unobjectionable'* and what this means within the Australian regulatory framework.
- The inclusion of a table to summarise the Order's requirements is a great idea to provide 'at a glance' requirement. However there are significant omissions which therefore make the table misleading has potential to be a very useful resource. We unfortunately haven't had the time to suggest a revised version and of course details may change. We believe this would be a valuable tool for industry and TGA evaluators and inspectors alike.
- The allowance that the Elemental impurities risk assessment process may allow sponsors and manufacturers to justify the absence of an impurity test in the finished goods specification MUST also be articulated in the Order. The Order represents the minimum quality standard, the inclusion of a specification for elemental impurities would otherwise be expected as a minimum standard reflected in the finished product specification. It is therefore important to avoid mandating unnecessary finished product testing, that this allowance is provided in the Order. ASMI have proposed revised wording in Sections 11 and 17 of the Order.

Summary and response to consultation questions

- **how the reintroduction of pills to the remade Order will affect your business**

The reintroduction of pills to the order does not impact any ASMI members.

- **if the 12 month transition period for the inclusion of pills is suitable**

ASMI is unable to comment of the suitability of the 12 month transition for pills.

However we advise that the impact of the changes implemented in TGO 101 are significant and will require a transition period of 2 years, which will require the remaking of TGO 78 without amendment for the period of the transition period.

- **which impurity limits should apply to medicines not following an individual monograph**

The requirement to choose between Option A (BP) and Option B (USP) for elemental impurities limits for herbal materials or herbal preparations, does not provide for harmonisation. In the absence of either PDEs within the Australian environmental context or an understanding of risk assessment outcomes of existing products, sponsors have no reference for an informed decision. We therefore suggest a combination of Option 1 and 2 would be more suitable i.e. adopting the limits of Option 1 for the majority of elements, however including the mercury limits as per option 2.

- **how the introduction of heavy metal limits in the remade Order will affect your business**

The introduction of heavy metal limits will impact all products without a specific monograph in the BP – the background to this are provide.

The impact of not providing a transition period for those products for which a risk assessment has not yet been completed is that manufacture and release of product will be required to cease until risk assessments are completed.

- **the suitability of the requirements specified in the remade Order**

The changes to requirements for dissolution for registered medicines with or without an applicable monograph is overly burdensome and will also require a 2 year period for transition requiring the

remaking of TGO 78 without amendment to ensure the ability to continue supply until the necessary changes are made.

The drafting of Sections 18 and 19 have introduced the mandatory requirement for disintegration testing of chewable tablets – and not a requirement of the default standards BP/EP or USP.

The omission of reference to one of the default standards where a test exists in that pharmacopoeia (particularly the BP the current requirement in TGO 78) will create administrative burden to the industry, requiring update to all test methods and specifications.

- **the exclusion of unapproved goods from the application of the remade Order**

[redacted]

- **the usefulness of the proposed guidance document**

[redacted]

- **suggested improvements to either document**

[redacted]

- **alternative options if you do not support the proposal**

ASMI have provided an alternate option to Option 1 and Option 2 for Elemental impurities and Residual solvent limits for goods containing herbal materials or herbal preparations in *Schedule 1 item 3*.

ASMI have also provided a proposal to extend *Schedule 2 – Tablet and capsules: assay limits for content of active ingredient or component in a tablet or capsule*.

- **an assessment of how the proposal will positively and adversely impact on you**

An assessment of the adverse impact on members has been provided in the event that the Order is implemented without an effective transition period of 2 years.