Technical Alert

Public Consultation Open: Remaking TGO 78 Standard for Tablets and Capsules as the new TGO 101. Changes to:

Default Standards for Finished Product

Impurities (Arsenic, Lead, Cadmium, Mercury)

Traditional Chinese Pills.

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Public Consultation Open: Remaking TGO 78 Standard for Tablets and Capsules as the new TGO 101.

On 1 April 2019, the Therapeutic Goods Order No. 78 Standard for Tablets and Capsules ('the Order') will sunset (it is automatically repealed by the Government 10 years after introduction). To remake the Order by 31 March 2019, the TGA have released a public consultation including a consultation draft of the proposed new document.

There are a number of proposed changes that will significantly affect listed and complementary medicines, as outlined in this alert.

Key Changes: Choice of Default Standard for Finished Product; & Impurities limits for all products

Current: In the TGO 78, if there is no individual monograph for a specific finished complementary medicine tablet or capsule in the British Pharmacopoeia, then the requirements of the TGO 78 apply.

Proposed: Under the new Order (Part 2, Division 1), a choice of default standard is provided, subject to additional conditions.

Listed and registered tablets and capsules have the choice of complying with:

- the ***Australian specific requirements*** as set out in the draft Division 3 of the Order; OR
- an ***applicable monograph***[1] in the BP, EP, or USP (subject to additional specific requirements).

[1] ***applicable monograph,*** in relation to therapeutic goods, means a default standard specified with reference to:

Listed and registered tablets and capsules may comply with the requirements specified in an ***applicable monograph***, subject to the additional matters specified in Division 2:

- **(s11) Folic Acid dissolution** if >100mcg folic acid; and
- **(s12) Impurities – applicable limits for Arsenic, Cadmium, Lead, Mercury** are set for registered and listed tablets and capsules with an applicable monograph, based upon that specific monograph, *or if none*, then any specific monograph in an applicable Pharmacopoeia to the product, *or if none*, then the limits in the applicable general monographs or general chapters apply. Note that the USP has applicable limits to dietary supplements:

  USP
  - **Dietary supplements chapter: *<2232> ELEMENTAL CONTAMINANTS IN DIETARY SUPPLEMENTS***
  - **General chapter: *<232> ELEMENTAL IMPURITIES—LIMITS***

  BP
  - General notice: *Pharmaceutical preparations*
  - Supplementary Chapter: *SC IV Q. Elemental Impurities*

  European Pharmacopoeia (Ph.Eur.)
  - General monograph: *Pharmaceutical preparations* (*2619)*

  Note that for the USP chapter <2232> provides three options for compliance with limits for elemental contaminants as specified below:

  - Analysis option – in this option the finished product is analysed to determine the elemental contaminant levels, and the amount present when taken at the maximum daily dose. This amount must not exceed the "Permitted Daily Exposure" (PDE).

(a)a formulated preparation in the British Pharmacopoeia;
(b)a preparation in the European Pharmacopoeia; or
(c)an official product in the United States Pharmacopeia-National Formulary;
whether or not those goods are labelled as conforming to that standard, and comprises:
(d)a specific monograph;
(e)one or more applicable general monographs; and
(f)one or more applicable general chapters;
interpreted in accordance with the General Notices section of the relevant pharmacopoeia.

Note 1: Subsection 3(1) of the Act provides that the default standard must be interpreted in accordance with the General Notices section of the relevant pharmacopoeia.

Note 2: Subsection 13(7) of the Act specifies how to work out whether therapeutic goods conform with a default standard at a particular time.

- Individual component option – this option may be used for products with a maximum daily intake of no more than 10g of the finished product. Individual component limits are described; for lead is stated as 0.5 mcg/g (or parts per million [ppm]).
- Summation option - this option may be used for products with a maximum daily intake of more than 10g, and those in which ingredients exceed the individual component levels (described above). The amount of each elemental contaminant from each ingredient is determined, and the total mcg/daily intake from the product must not exceed PDE values.

The individual component approach is an option for compliance with the PDE value, which is the limit that applies regardless of the whether the maximum dose is greater than or less than 10g.

Products with a maximum daily intake of less than 10g of the finished product could apply a higher limit than 0.5 ppm as long as the maximum daily exposure to impurities from the product falls below the PDE limit; this can be determined using the summation option.

- **(s13) Dissolution** – certain registered tablets and capsules without folic acid must comply with a dissolution test if there is one applicable to the active ingredient in any default standard.
- **(s14) Uniformity** – listed medicines who choose to comply to an applicable monograph may substitute a uniformity test in the monograph with the uniformity test specified in Schedule 1 of the draft Order.

Alternatively to the above requirements, listed and registered tablets and capsules may comply with the ***Australian specific requirements*** in Division 3 under this proposal:

- **(s15) Assay limits for active ingredients**.

  For *listed* medicines, these are **unchanged** from TGO 78 generally at **90 – 120%.**

  For *registered* medicines, these are **expanded** to **90 – 110%,** up from 92.5 – 107.5%.

  For *listed* medicines, the limits for vitamins/provitamins, minerals and mineral compounds, enzymes, and probiotics are **unchanged** from Schedule 1 of the TGO 78 (now included in Schedule 2 of the Order), but it is now proposed that the limits will also apply to *registered* medicines with those active ingredients.

  Other content requirements remain the same, such as two or more components that vary independently of each other is not less than 90%, etc.

- **(s16) Folic Acid dissolution** if >100mcg folic acid.
- **(s17) Impurities - applicable limits for Arsenic, Cadmium, Lead, Mercury**

  The Australian specific limits adopts the limits from a specific monograph to the tablet or capsule, if such a monograph applies and has applicable limits for these impurities, otherwise the proposed Order requires that all listed and registered tablets and capsules comply with the following:

2	impurities	(a) for **arsenic**— a maximum concentration of **1.5 parts per million**; (b) for **cadmium**— a maximum concentration of **0.5 parts per million**; (c) for **lead**— a maximum concentration of **0.5 parts per million**; (d) for **mercury**— a maximum concentration of **3 parts per million**; (e) for **residual solvents**— the limits specified in **European Pharmacopoeia (5.4);**
3	impurities for goods containing herbal materials or herbal preparations	**OPTION 1 for consultation** (a) for **arsenic**— a maximum concentration of **2 part per million**; (b) for **cadmium**— a maximum concentration of **1 parts per million**; (c) for **lead**— a maximum concentration of **5 parts per million**; (d) for **mercury**— a maximum concentration of **0.1 parts per million**; (e) for **residual solvents**— the limits specified in **European Pharmacopoeia (5.4)**; **OR** **OPTION 2 for consultation** (a) for **arsenic**— a maximum concentration of **1.5 parts per million**; (b) for **cadmium**— a maximum concentration of **0.5 parts per million**; (c) for **lead**— a maximum concentration of **0.5 parts per million**; (d) for **mercury** (**total**)— a maximum concentration of **1.5 parts per million**; (e) for **methyl mercury (as Hg)**— a maximum concentration of **0.2 parts per million**; (f) for **residual solvents**— the limits specified in **European Pharmacopoeia (5.4);**

- **(s18) Dissolution** – specific requirements for Registered medicines, and for all tablets and capsules that are modified- release (no change to existing requirements).
- **(s19) Disintegration** – for all tablets and capsules that are not subject to dissolution under s18, then the disintegration test in either the European Pharmacopoeia (2.9.1) or United States Pharmacopoeia-National Formulary, chapter <701> applies.
- **(s20) Fineness of Dispersion** – the test in the BP general monograph "Tablets" as per existing arrangements.
- **(s21) Uniformity of Weight** (mass) – For listed medicines, European Pharmacopoeia (2.9.5) or United States Pharmacopoeia-National Formulary, chapter <711>.

  For registered medicines, uniformity of dosage units requirements apply as per European Pharmacopoeia (2.9.40) or United States Pharmacopoeia-National Formulary, chapter <905>

(Traditional Chinese) Pills

Part 3 of the proposed new Order applies to pills. Currently, the only pills on the ARTG are Traditional Chinese Medicines.

The new Order aligns physical tests for pills from the Pharmacopoeia of the People's Republic of China.

Impurities - Impacts on Industry

Further discussion on impurities limits will be provided in a future alert.

In the interim CMA welcome your feedback on the new Order and in particular the impurities limits proposed in developing the industry-wide submission, particularly:

- Expected Costs to be incurred;
- Expected impact on products, or product losses;
- Other impacts or views.

Please send any communication regarding the proposed TGO 78 and the impurities limits to Lucy.Lang@cmaustralia.org.au

Consultation Links

Announcement and general information from the TGA here.

Draft new "TGO 101" (to replace the TGO 78):

- Draft: Therapeutic Goods (Standard for Tablets, Capsules and Pills) (TGO 101) Order 2019 (pdf,219kb)
- Draft: Therapeutic Goods (Standard for Tablets, Capsules and Pills) (TGO 101) Order 2019 (pdf,135kb)

Consultation Documents:

- Consultation: Remaking Therapeutic Goods Order No. 78 - Standard for Tablets and Capsules and reintroducing pills into the remade Order (pdf,2.20Mb)
- Consultation: Remaking Therapeutic Goods Order No. 78 - Standard for Tablets and Capsules and reintroducing pills into the remade Order (docx,2.33Mb)

Draft Guidance for TGO 101:

- Draft: Guidance for TGO 101: Standard for tablets, capsules and pills (pdf,406kb)
- Draft: Guidance for TGO 101: Standard for tablets, capsules and pills (docx,115kb)

Individual Business' Submission to the TGA

The outcome of this Consultation will depend on submission received. CMA encourages all businesses to make submissions to the TGA in relation to this consultation.

The TGA are inviting submissions that may include:

Submissions may include your information on (CMA highlights added):

- how the reintroduction of pills to the remade Order will affect your business
- if the 12 month transition period for the inclusion of pills is suitable
- which impurity limits should apply to medicines not following an individual monograph
- how the introduction of heavy metal limits in the remade Order will affect your business
- the suitability of the requirements specified in the remade Order
- the exclusion of unapproved goods from the application of the remade Order
- the usefulness of the proposed guidance document
- suggested improvements to either document
- alternative options if you do not support the proposal
- an assessment of how the proposal will positively and adversely impact on you.

ENDS