



Mr Michael Smith
Head
Office of Complementary Medicines
Therapeutic Goods Administration
GPO Box 100
WODEN ACT 2600

Dear Mr Smith

Re: Therapeutic Goods Order No. 78 – Standards for Tablets and Capsules

I refer to your letter dated 25 January 2010 and thank you for providing an opportunity for the complementary medicines industry to comment on the resolutions from the Therapeutic Goods Committee (TGC) 35th meeting in relation to the *Therapeutic Goods Order No. 78 – Standards for Tablets and Capsules* (TGO78).

The Complementary Healthcare Council (CHC) notes that the proposed redrafted version of TGO78 has not been provided to industry; only the principles have been outlined in detail. The CHC provides comments based on industry's interpretation of these principles and how they would be applied to TGO78. Any necessary drafting that may occur as a result of this consultation should be done in complete consultation with the CHC and its members.

It is noted that the intention of the proposal was to provide alternative pharmacopeia's for industry however it seems that the outcome will be a requirement for compliance of all the pharmacopeia's rather than the option to choose.

The CHC strongly opposes the recommendation made by the TGC for the United States Pharmacopoeia – National Formulary (USP-NF) to be given equal status to monographs of the British Pharmacopoeia (BP) due to the significant negative impact on industry with regards to dissolution testing requirements; from both a cost and compliance perspective. The CHC does not believe that dissolution testing, as per the USP-NF, will show any significant advantage to the end consumer over disintegration testing which is currently performed on most complementary medicines.

The products classified as complementary medicines in Australia are known as dietary supplements within the United States (US). The requirement for Good Manufacturing Practice (GMP) in the US is considered to be inferior when compared to that of the medicine standards within Australia. Moreover, the US regulatory framework for dietary supplements is also perceived to be less robust than that of the TGA. Considering these important differences in regulation requirements for dietary supplements compared to complementary medicines in Australia, it is understandable that the USP-NF would require dissolution testing of such products to test for integrity. However, in Australia, complementary medicines are exposed to a high standard of GMP and regulation which ensures the integrity of these products quality, efficacy and safety. For these reasons, it does not seem necessary to require dissolution testing of complementary medicines in Australia through adoption of the USP-NF in TGO78.

Implementing the proposed recommendation may severely disadvantage Australian companies who export overseas to various countries (not including export only listings). Currently US dietary supplements do not need to comply with the relevant USP monograph when it is not specifically claimed as a 'USP standard

product' on the label. The CHC does not support any recommendation that would disadvantage Australian companies international trading.

Finally, the CHC would also like to draw to your attention that discussions relating to dissolution testing have been raised previously through the Office of Complementary Medicine/Industry Consultative Group (OICG), as well as through calls for comment under the proposed joint regulatory agency – *Draft Managing Director's Order "General Requirements for Tablets and Capsules"*. Through these discussions, it was agreed between the regulators and industry that the requirement for dissolution testing for complementary medicines would not be applied. Given the previous discussions which were detailed in nature, the CHC does not believe there is 'new' justification for raising this issue again for further discussion and questions why the Office of Complementary Medicine (OCM) brought the matter to the TGC for consideration?

1. Listed medicines – dissolution requirements.

Cost implications

It has been noted by CHC members that if the USP-NF is adopted as part of TGO78, the biggest impact will be the additional costs which will inevitably be passed on to consumer. Dissolution testing will place a large burden on complementary medicine manufacturers with no apparent added safety or quality benefits. The CHC considers that the negative impact of this recommendation outweighs the benefits for implementation of this provision.

An analysis has been conducted by one particular complementary medicine company (*refer to Attachment 1*) which estimates that up to 240 products may be affected by this recommendation. A second manufacturer has estimated that approximately 900 additional batches per year, involving about 200+ products, may be captured under the dissolution testing provision. The estimated costs are similar to that outlined in Attachment 1). The additional testing and validation costs associated with the implementation will be significant. In addition, there would be further costs associated with resourcing (staff) and additional equipment requirements to accommodate the new testing procedures. The CHC is concerned that all of these additional costs will have a large impact on industry from both a monetary value as well as an increased workload volume.

Companies will be required to purchase the necessary equipment (dissolution machines) to perform the testing or alternatively send the products out for external testing. Members have advised the CHC that each dissolution apparatus costs approximately \$25,000; in many cases, more than one piece of apparatus would be required. Furthermore, additional UPLC/HPLC's may also need to be purchased which range in price from \$100,000 to \$140,000. Add on to this, costs for service contract obligations and consumables, another \$20,000 to \$50,000 would need to be factored in to the overall costs.

In addition to resourcing and equipment, other costs which would significantly impact industry include method validation, documentation set-up, and any required product reformulations that might be driven by failed dissolution results. This extra testing would also significantly lengthen the lead time for product formulation and release for sale. It has been estimated that to meet the new requirements, additional staffing costs to perform the testing, reformulation and validation testing could be up to \$230,000.

With the new requirements for dissolution testing, another factor which impacts industry is stability. All products which undergo dissolution testing, would be required to undergo stability testing; noting that dissolution would be carried out at various time points throughout the stability program. This is a substantial cost to any complementary medicine company.

Reformulation implications

Reformulation of existing products may be required to ensure compliance with the dissolution requirements throughout the product's shelf life. Members have advised that while it is possible for the product to pass at time = 0, there can be issues with maintaining compliance with dissolution requirements as the product ages. Given this, the CHC questions the usefulness of the dissolution testing results?

Assay Limits Implications

The CHC notes there are many inconsistencies between the limits prescribed within the monographs found in the USP-NF when compared to the current TGO78. The introduction of new or different limits will require additional testing of products to ensure they comply. It is understood that companies could apply for a Section 14 Exemption however the TGA would most likely be inundated with applications for popular ingredients which would take up valuable resources with again, no clear benefit to consumers.

The assay limits outlined in TGO78 under Section 10 Listed tablet or capsules without an individual British Pharmacopoeia monograph, has taken into account the natural variation of ingredients from natural origin which is highly relevant to complementary medicine ingredients. However, assay limits prescribed in the USP-NF monograph do not seem to have taken the same approach. An example is *Fish Oil Containing Omega-3 Acid Capsules*.

In the BP monograph, fish oil (raw material) is prescribed with **no upper limit** for omega-3 fatty acids (i.e. EPA and DHA). In the USP-NF monograph, the assay limit is prescribed as **95 to 105%** for the omega-3 fatty acids. In the current version of TGO78, the prescribed limit is **not less than 90%** for omega-3 fatty acids.

The statement 'They may contain other labelled added substances that are generally recognised as safe, in amounts that are unobjectionable'.

The CHC does not support the above statement as it is only applicable to the substances recognised in the US as 'GRAS', not the substances that are suitable for listing in Australia.

It is also noted that this 'catch all clause' comes with a requirement for compliance with TGO78 for other unobjectionable substances. This is not consistent with the TGA's stance on 'cherry picking' parts of monographs to suit industry.

As an example of issues with this clause, a list has been provided where this 'catch all clause' would apply:

- Calcium with Vitamin D tablets
- Calcium and Vitamin D with Minerals tablets
- Minerals capsules
- Minerals tablets
- Water-soluble vitamins capsule
- Water-soluble vitamins tablets
- Oil-soluble vitamin capsules
- Oil-soluble vitamin tablets
- Oil- and water-soluble vitamin capsules
- Oil- and water-soluble vitamin tablets
- Oil- and water-soluble vitamins with minerals capsules
- Oil- and water-soluble vitamins with minerals tablets
- Water-soluble vitamins with minerals capsules

- Water-soluble vitamins with minerals tablets
- Zinc and Vitamin C lozenges.

The CHC notes that the applicability of the monographs for the above mentioned products is broadened considerably. For example, Vitamin C, Zinc and Echinacea tablets would require dissolution as it falls within the definition of water-soluble vitamins with minerals tablets monograph. The CHC points out that the USP-NF monographs will capture a large variety of these types of products and not only those listed in monographs. It should also be noted that the list above is much longer than presented here in this submission; this list is provided only as an example. Once again, this emphasises the great burden to industry in adopting the USP-NF.

USP's Dietary Supplement test for weight variation

The proposed weight variation test in place of the current uniformity of dosage unit requirement is inconsistent with TGO78. The CHC considers there is no justified reason to change the requirement.

USP-NF Complementary Medicines finished Product monographs

To demonstrate the number of finished products that would be captured by the provisions within the USP-NF, the CHC has provided a list as *Attachment 2* to this submission. This list is quite significant again demonstrating the regulatory impact on industry.

2. Pills

The CHC notes the proposal to extend TGO78 to include 'pills' as per the requirements of the *Pharmacopoeia of the People's Republic of China 2005 (volume 1)* (CP). The CHC is unwilling to support this proposal at this stage, particularly without viewing the wording which would be included in TGO78.

The CHC is not clear as to what the need is for an exception to be in place for physical testing (not chemical or microbiological) for all Traditional Chinese Medicine pills, noting that sponsors have previously complied with the requirements of the TGO for tablets and capsules. The CHC questions whether this proposal is in response to non-compliance by Traditional Chinese Medicine companies to TGO78 (or the superseded versions)? The CHC also questions whether the recommendation is due to our current regulatory requirements being too complex and unique for imported goods?

The CHC notes that 'pills' are defined within TGO78 and that there are no imposed requirements thereafter. However, according the CP, 'pills' may be honeyed, water-honeyed, watered, pasted, waxed, concentrated, dripping pills, and less than or greater than 0.5g each. The CHC considers that a simple reference to 'pills' is inadequate and that a clear definition would need to be provided before the complementary medicine industry would support the recommendation.

The CHC believes further consideration should be given to a modification of the requirements within TGO78 rather than adopting the CP as a default standard for listed pills of the types described. The CHC considers adopting the CP will 'open the door' and that robust discussions is needed to determine the possible implications of this recommendation.

Summary

In summary, whilst the CHC is not opposed to the adoption of the Ph. Eur. as an additional default standard for TGO78, there is currently no support for the adoption of the USP-NF due to the significant impact to industry without a well defined benefit to consumers. The CHC does not believe the recommendation in relation to dissolution testing is in keeping with the COAG principles of minimising regulatory burden and implores the TGA to reconsider accepting the recommendation put forward by the TGC.

Furthermore, the CHC does not support the additional proposals relating to the 'catch all clause', the weight variation or the inclusion of pills to TGO78.

If you would like to discuss anything within this submission further, please do not hesitate in contacting me further.

Yours sincerely

A handwritten signature in black ink, appearing to read 'Kristy Tomas', written in a cursive style.

Kristy Tomas
Scientific & Technical Manager

9 February 2010