CMA Submission to the TGA Consultation:

Consultation on adoption of European Union guidelines in Australia: ICH Q3D for listed & herbal medicines.

To:

Therapeutic Goods Administration

PO Box 100

WODEN ACT 2606

via

euguidelines@tga.gov.au

complementary.medicines@health.gov.au

From:

Complementary Medicines Australia

PO Box 450

MAWSON ACT 2606

Telephone: 02 6260 4022

E-mail: carl.gibson@cmaustralia.org.au

Website: www.cmaustralia.org.au

April 29, 2019

Consultation

The TGA are seeking comment on the proposed adoption of the EU guidelines as follows:

Quality guidelines

Impurities

CHMP/ICH/353369/2013 (pdf,822kb)*

ICH Q 3 D Impurities: guideline on elemental impurities
Effective date: 25 July 2016

> **TGA Annotation:**
> Although the guideline states in Section 2 that it does not apply to herbal products, **in Australia the guideline has been adopted for all herbal medicines including listed medicines.**

The consultation information contained very little by way of clarification of this extremely large and potentially high impact proposal, of the rationale, or the implementation. Nor did it describe why it was being proposed for herbal products when these are not within the scope of the proposed guideline.

Further, it did not include the legal mechanism by which it is proposed that the guideline would be adopted for listed medicines. Prior advice from the TGA is that:

> "The use of European Union (EU) and ICH guidelines adopted in Australia and other Australia-specific guidelines is not mandated in the legislation in relation to listed medicines. Therefore the requirements specified in an EU guideline cannot be enforced unless failure to meet requirements in the guidelines also results in a breach of Australian Therapeutic Goods legislation."

An enquiry marked high importance was sent to the EU Guidelines Coordinator on 20 March 2019, providing the above information and therefore seeking clarification on the legislative mechanisms and proposed transition periods, without response.

At a separate meeting in April 2019 it was provided that the possible legal options were a condition of listing (section 28 of the Act) or via a new legislative instrument. CMA industry representatives provided the view that adoption of a drug guideline that specifically excludes its relevant applicability to herbal medicines is not appropriate to apply to listed herbal medicines.

Response to Consultation

1. **Adoption of guidelines for classes of medicines must only occur when those guidelines are designed appropriately for those classes of medicines. This guideline is not applicable to herbal products.**

   The scope of the ICH Q3D is very clearly distinguished as to its inclusions and exclusion criteria. It distinguishes clearly between 'drug products' and herbal products by the definitions referred to in Q3D by cross reference to Q6A and Q6B. Herbal products are specifically excluded from the scope of the document:

   > '**This guideline does not apply to herbal products**, radiopharmaceuticals, vaccines, cell 41 metabolites, DNA products, allergenic extracts, cells, whole blood, cellular blood 42 components, **crude products of animal or plant origin**, [etc]'.

   The complementary medicine sector is opposed to the introduction of guidelines that are not intended nor designed for that product class. There are a number of technical issues for herbal products as they relate to certain impurity types and detection methods that support that this document is not suitable for herbal medicines as referred to in our February 2019 submission regarding elemental impurities for TGO 101 (CMA Submission - Remaking TGO 78).

   - **Consultation submission:** CMA strongly opposes the adoption of a mandatory quality requirement for herbal medicines (the ICH Q3D) that is specifically not designed for herbal medicines, as an inappropriate policy and technical approach. It is not suitable to make the Q3D, as a document not designed for herbal medicines, as a mandatory requirement for herbal medicines.

2. **The proposed adoption of ICH Q3D is a doubling of requirements for listed tablets / capsules / pills of the TGO 101 who must comply with the requirements of TGO 101 and choose to apply the requirements of USP <2232>.**

   The USP <2232> and the ICH Q3D would not be applied simultaneously logically. The proposal to apply the ICH Q3D as a mandatory requirement overrides the ability of manufacturers of tablets, capsules and pills to genuinely make the choice as per TGO 101 to apply the appropriate requirements of the USP <2232>.

   - **Consultation submission:** CMA strongly opposes the adoption of a mandatory quality requirement that, by its simultaneous application, would override the choice available within an existing standard (TGO 101) for listed tablets, capsules, and pills. It is not logical to implement an approach that is not compatible with the newly implemented TGO 101 ability to choose ***either*** "USP <2232> ***OR*** the ICH Q3D" for tablets and capsules (with the USP as the better and preferred approach in most cases for this class of medicines).

3. **There must not be an inconsistent technical approach to elemental impurities between tablets / capsules / pills and other dosage forms.**

   The industry response to TGO 101/Remaking TGO 78 for tablets, capsules and pills specifically identified the USP <2232> as the most appropriate technical document for impurities in listed medicines, particularly in relation to herbal medicines. The submission also noted that some listed medicines (particularly non-herbal products) may have a preference for the ICH Q3D depending upon the facility and the product type, however that it should only be an equal but alternative option to the primary preference of USP <2232>. This discussion was included in the February 2019 submission, the same principles apply to other dosage forms that are listed and herbal medicines.

   - **Consultation submission:** Proposed requirements for all listed medicines must not be inconsistent between different dosage forms where there is not any regulatory rationale

to do so. Any such proposal must, via a full and proper public consultation, be harmonised with existing standards for the same class of goods. The points in the submission in February 2019 that has already been made outlining the preferences for standards for listed medicines including herbal products continue to apply.

4. **Routes of administration that are not oral. Full consideration has not been given to the rationale behind proposing this approach to "all" listed medicines including herbal medicines.**

   - **Consultation submission:** The consultation has not adequately considered the rationale behind applying this requirement to "all" listed medicines, including which routes of administration are relevant to the purpose of the guideline. It does not require application to many topical skin products and other routes of administration, resulting in regulatory burden and increased costs for consumers without purpose.

5. **Transition period.** The process of adopting the USP <2232> *or* ICH Q3D for listed medicines is a vast process for the many thousands of products on the register. This is not merely a process of introducing risk assessments, which in itself is an enormous task across large contract manufacturers, the outcomes of those assessments will require new management plans and considerations put into place. Associated testing may be required, and manufacturers are continuing to determine the extent of requirements for additional laboratory space (a multi-year process), hiring of technical staff, and additional capacity at contract laboratories, with associated at 'large-scale' considerations including the ongoing availability and cost-effectiveness of required testing substrate materials (high cost argon gas), etc. This is a long, multi-year process. Three years is the minimum, for both domestic and international manufacturers, particularly considering the extra time for listed medicines other than tablets, capsules, and pills may be needed following the two year implementation in the TGO 101.

   For some products particularly herbal products, there will be additional supply chain considerations that go back to the source of the ingredients to the international growers and suppliers of herbal materials. Herbal materials are often a 12-36 month growth cycle and

involves complex processing considerations. Further, the same testing concerns as above may apply.

- **Consultation submission response:** A genuine three year transition period is imperative for the reasons as outlined above and the February 2019 submission, including 12 months over and above to permit prioritisation of tablets and capsules.

Conclusion

CMA appreciates the ability to comment in relation to this proposal; but notes that there are serious flaws in the proposal that necessitate strong opposition to the proposed adoption:

- The consultation is inadequate, and the legal mechanism is not described, nor the effects upon different types of products;
- Transition periods have not been considered or described, including in relation to the current implementation of TGO 101 requirements;
- The proposal includes herbal products which are not within the scope of the proposed guideline;
- The ICH Q3D is the far less appropriate standard in relation to listed and herbal medicines in many circumstances when compared to the USP <2232>;
- The proposal would override and therefore reduce the choice and significantly heighten the regulatory impact on manufacturers implementing the TGO 101 for tablets, capsule, and pills;
- The proposal creates an unnecessary divide and confusion between different dosage forms and regulatory documents, despite the lack of relevance of the dosage form;
- Applicable routes of administration, which are relevant, have not been considered in relation to suitability of applying the proposal.

Please do not hesitate to contact us directly in relation to clarification, questions, or further discussion on these matters.