The Clearance Coordinator
Office of Manufacturing Quality
PO Box 100
WODEN ACT 2606

Dear Clearance Coordinator,

Re: Comment on GMP Clearance for Overseas Manufacturers

Thank you for the opportunity for the complementary healthcare industry to provide comment on the September 2010 draft of the Australian Regulatory Guidelines for the GMP Clearance for Overseas Manufacturers.

The Complementary Healthcare Council (CHC) notes the current draft represents the outcome of several earlier versions which have been worked on by representatives of industry associations including the CHC. Overall, the CHC considers the document has greater readability and includes useful website links for users.

General Comments

The CHC would like to raise the following comments for consideration:

1. There does not appear to be guidance in relation to US FDA medicine GMP certification not being accepted by the TGA for complementary medicines. The CHC suggests that it would be useful to include this in the relevant sections within the document.

2. The term GMP Contract and GMP Agreement seem to be interchangeable throughout the document and are grouped as such in the glossary of terms (Appendix A). The CHC suggests that only one term be used throughout the document for consistency.

3. The *Note* on pages 14 and 29 which states: '*A TGA on-site audit will always be required where the sponsor's listed or registered medicine is not regulated by the regulatory agency of the country in which the manufacturing site is located*' is not consistent with Table 1(a), which allows for Compliance Verification of a MRA Regulator outside of own country.

Specific Comments

The CHC provides the following specific comments for consideration:

1 - Introduction:

- Page 4, paragraph 3: The CHC notes that the TGA Office of Medicines Authorisation does not issue a Market Authorisation for therapeutic goods that are exempt from the requirement for inclusion into the Australian Register of Therapeutic Goods (ARTG). It is not clear as to whether sponsors of such products need to obtain preclearance if they are manufactured overseas.

- Page 4, footnote 1: The CHC suggests rewording this section to read "*Under the Therapeutic Goods Act 1989, some therapeutic goods are exempt from the requirement to be registered on the ARTG*".

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- Page 5, paragraph 5: '*The TGA reserves the right to undertake an audit of an overseas manufacturing site, irrespective of any evidence supplied'*, should be amended to read '*the TGA reserves the right to undertake an audit of an overseas manufacturer if the TGA believes the evidence supplied is inadequate'*. The statement as it currently reads does not specify under what conditions the TGA will audit when evidence has been provided.

- The statement concerning GMP Clearances outlined on page 5, advises sponsors to monitor the expiry date of GMP Clearances for all overseas manufacturers used and submit applications before the current GMP Clearance expires. It is suggested that a side note be added to advise that the TGA's current process is to send a Section 31 letter alerting sponsors three months before their GMP Clearance is to expire.

- Page 6, last paragraph: The CHC suggests the paragraph be reworded to remove the reference to 'Association of Therapeutic Goods Consultants Inc' noting that there are a number of industry associations which can provide relevant information. The sentence could be reworded to, "*Further details concerning agents or consultants can be obtained from various relevant therapeutic goods industry associations*".

2 - Responsibilities of Australian sponsors of medicines manufactured overseas:

- This section does not clarify whether a contract is required between a parent company and its affiliate. The CHC notes that such guidance is referred to in Appendix C and that a side note on page 31 of the document, advising users to refer to Appendix C, would be useful.

- Page 7, dot point 4: All required documents are to be submitted electronically by the sponsor. Although the sponsor is not expected to have a GMP agreement with a sub-contractor of a manufacturer, a GMP agreement has to be in place between the manufacturer and their sub-contractor. The sponsor is responsible for ensuring that it exists and is current. Hence the sponsor needs to either review or have in their possession a copy of such an agreement. It is unclear whether the sponsor needs to include such a GMP agreement in the set of documents submitted to the TGA by the sponsor. If the manufacturer and the sub-contractor are in Australia, the TGA allows the manufacturer to hold the documentation without the sponsor having viewed the document. The CHC stresses that a level playing field is needed for these two situations.

3 - GMP Clearance process:

- Page 9, Steps 3.5 and 3.6: It is unclear how long the TGA Office of Manufacturing Quality (OMQ) will take to close out an audit once all deficiencies are closed out. The timeframe for OMQ to issue reports is unclear; the CHC considers it would be useful to have a time period stated for the benefit of industry.

    - The CHC notes that the TGA will reject applications if information is not supplied within the due dates however, questions what mechanisms are in place to ensure the TGA remains accountable should the agreed target timeframe not be met?

3.1 GMP Clearance application requirements:

- The CHC notes there is not a requirement for listable and most registerable Active Pharmaceutical Ingredients (API) to be manufactured in TGA licensed facilities; this is mandatory only for prescription medicine APIs. The CHC therefore, considers it may be difficult for Australian sponsors purchasing APIs through Australian agents, to demonstrate they have been manufactured in a TGA

licensed facility, especially for multi active products. The CHC suggests this issue be discussed further and suitable guidance be included.

- Page 10, second paragraph at 3.1: This section requires further clarification as it may be interpreted to mean that the TGA does not require sponsors to submit applications for APIs for listed medicines. The CHC understands that sponsors of APIs need to ensure they are manufactured in a TGA licensed facility. To provide further clarity for industry, the CHC suggests the sentence be separated out to 1) explain that sponsors are responsible for ensuring manufacturing outside of Australia is conducted in a TGA licensed facility, and 2) explanation of situations where APIs are exempt from manufacturing within a TGA licensed facility.

- Page 10, GMP Clearance paragraphs 1 and 2: It is noted that APIs made in Australia for use in the manufacture of registered medicines must be manufactured in a TGA licensed facility. There is an inequality in that overseas manufacturers of APIs for use in listed medicines are not subjected to the GMP Clearance process. However, sponsors must ensure that any step in manufacture undertaken outside Australia is done in a TGA licensed facility.

  This means:
  - Sponsors of listed medicines will have to hold evidence that the APIs manufactured overseas for use in listed medicines are manufactured in a TGA licensed facility. The CHC questions how achievable it will be for sponsors to obtain this evidence. If the information cannot be obtained, is a responsible sponsor unable to use such APIs in listed medicines? If not, the CHC points out that the listed medicine industry in Australia will be greatly impacted.

  - Excipients are currently exempt from this requirement. If the TGA is concerned about contamination within substances used in medicines, should the requirement apply equally to APIs and excipients?

  - It is unclear how the TGA will ensure that all sponsors hold relevant information since they do not audit sponsors who are not manufacturers. Further guidance is sought around this point.

- Page 10, Renewing a GMP Clearance: It is noted that the TGA is currently 'backlogged' with regards to processing overseas GMP audits due to additional auditing requirements as per the new 2009 Code of GMP i.e. sunscreen manufacturers are now required to be audited. Knowing this, if a sponsor applies for a GMP Clearance renewal along with the associated GMP audit, but the TGA audit is not conducted within the expiration period of the GMP Clearance (e.g. the GMP Clearance lapses before the audit is conducted), the CHC believes that the TGA should automatically extend the GMP Clearance, as long as the application has been provided to the TGA within an acceptable timeframe (e.g. between 3 to 6 months of the expiration date of the GMP Clearance). The CHC requests that the TGA provide for this exception in the guidance document.

- Page 11, first dot point and section on Extensions of a GMP Clearance: Overseas manufacturers will need to ensure that all GMP Clearances issued to sponsors using that manufacturer, have their GMP Clearances scope expanded to include any new steps in manufacture. The CHC notes there can be considerable delays in issuing a final report once a TGA GMP audit has been completed and it is possible that GMP Clearance extensions will need to be sought whilst waiting for the final TGA GMP audit close out. The CHC suggested that a side note to inform industry of this would be beneficial.

3.2 GMP Clearances issued under a Mutual Recognition Agreements (MRA):

- Page 12, paragraph 1: states the conditions of when the TGA will accept compliance of an overseas manufacturer with local GMP standards. This section should also include that a current certificate of GMP compliance for the manufacturer from the competent regulatory authority is required.

- Page 13, GMP Clearance issued through GMP Compliance Verification (CV): It may be useful to define what overseas regulatory agencies are regarded as competent by the TGA or confirm that the list at the top of the third column in Table 1(a) comprises the full range of such competent agencies. This also applies to the comment entry on Page 16 about the GMP Certificate alternatives. However, the note at the end of Table 1(b) states that the TGA may still conduct an audit of such contract laboratories even if they have acceptable certification. The CHC notes that this may cause uncertainty in many overseas countries, including New Zealand. It is noted that the Glossary of Terms on page 26 is similarly unclear about the competent regulatory authorities.

- Page 13-19, Section 3.3: The CHC notes this is a new section and that the layout is very useful for industry. However, this section does not specify whether the 'current certificate' is required to be notarised. If this is the case, the CHC suggests it be included into this section of the document.

- Page 15, Table 1(b) – Documentary evidence requirements, under the column - Evidence list B and Evidence List C: the terms used should be consistent with the terms used in Table 1(a) – Required Assessment type.

- It is suggested that Tables 1(a) and (b) outline the requirements for listed and registered medicines and Tables 1(c) and (d) for prescription medicine APIs, Contract Test Laboratories and Sterilisers. Table 1(a) and (b) in the current draft is made more complex by the addition of APIs.

- Page 16, Evidence List D:
    - Comments about GMP Certificate alternatives: It is noted that overseas contract testing laboratories can undertake testing for on-going stability as well as testing for Release for Supply. Similarly, the TGA Questions and Answers document (Question 44), allows for the use of a range of alternatives for on-going stability testing laboratories. However, there does not seem to be a mention of this range of alternative laboratories performing Release for Supply steps in manufacture on the TGA Website. The CHC suggests this be amended.

    - List of tests a contract testing laboratory is authorised to perform: It is unclear who performs the authorisation. Is the authorising agency the same as the competent authorities discussed above? If not, what criteria are needed to assess competency to issue the authorisation?

    - In relation to botanical ingredients: It is unclear if a copy of an appropriate Standard Operating Procedure detailing the procedure for tracing back to authenticated reference standards plus a register of all such traced botanical ingredients is adequate documentation to be submitted.

    - Contract sterilisers – in regards to GMP contracts (under comments/exclusions in the second last box) it does not state that a copy of the agreement between the manufacturer and contract steriliser should be submitted. Furthermore, there is no clarification of the requirements for sterilisers which would be useful to include in the guidance document.

- Page 17, currency of GMP certificates: the CHC notes that historically, some GMP certificates were valid for three years; the TGA would notify those expiring within 6 months of requesting a TGA Clearance not to submit an application, this practice has now changed to two years. The CHC queries the reason for the change.

- Page 17 states that the TGA can request certified copies of original documents at any time. The CHC suggests that further clarification be included on this for e.g. is it necessary to have the copy submitted electronically, certified as the original copy? In addition, if original certified copies will be requested in special circumstances, further guidance is needed on what defines a 'special circumstance'.

Documents for TGA on-site Audit:

- Page 18, Site Master File (SMF): Guidance is needed in the document to stipulate that sponsors will need to ensure that their overseas contract manufacturer provides a current, up-to-date SMF.

- Page 18 last sentence: It is unclear if the list of products (with batch numbers) manufactured over the two year period for supply into Australia (that will be required for a TGA re-audit), refers only to products made for that sponsor where re-clearance is being sought or for all sponsors. This clarification needs to be added to the section.

Sharing of documentary evidence between sponsors and manufacturers

- Page 19, Sharing documentation, last paragraph: It is noted that the system to share documentation applies to the Compliance Verification process. The CHC requests further consideration to whether a similar system could be applied to GMP Clearance approval activities based on a MRA arrangement or TGA audit process. For example, manufacturers in New Zealand will have to undergo repeated TGA on-site audits as neither of the other two processes is yet available.

4. Maintenance of a Clearance

- Page 24:
    - Footnote: The use of a TGA acceptable form would be of great benefit to industry. The CHC requests further information on the timeline for availability of such a document.

    - The last line of the introduction should reference pages 7 and 8 not pages 6 and 7.

Appendix B – International Agreements

- Page 29 - 30, other international agreements, last sentence above the table on page 29: It is noted that New Zealand is not a PIC/s country yet and that the Memorandum of Understanding that exists between the TGA and Medsafe, may or may not be applied to any particular situation. Hence, sponsors may think they have to apply for a formal TGA audit when it may be possible to apply for GMP Clearance based on Compliance Verification. The CHC requests that the TGA clarify its position about New Zealand manufacturers and laboratories and include into the document.

Additional Comments

The issue of overseas contract manufacturers with multiple Australian sponsors is not mentioned in the current draft guidance document.

The CHC suggests that details be provided to sponsors regarding:

- when overseas audits are conducted;
- Who 'owns' the licence?;
- What are the requirements if a new sponsor would like to have an overseas manufacturer cleared, if the audit has been paid by another sponsor.

The issue of 'no other choice than the TGA on-site audit' for complementary medicines in the US is a concern to the CHC. In such circumstances where the manufacturing site also makes OTC products and has the same Quality Management System for their complementary medicines, the site should require only Compliance Verification.

While the CHC notes that no guidance document can cover every aspect or question that industry may have, the comments within this submission are considered relevant and of importance to the complementary medicine industry.

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

Yours sincerely

Kristy Tomas
Scientific & Technical Manager

15 November 2010