CHC Submission to Therapeutic Goods Administration on Guidance on Release for Supply for Medicines Manufacturers

To:
Management & Coordination
Office of Manufacturing Quality
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606
gmp@tga.gov.au

From:
Emma Burchell
Head, Regulatory Affairs
Complementary Healthcare Council of Australia
PO Box 450
MAWSON ACT 2607

Date:
6 September, 2013

Introduction

The Complementary Healthcare Council of Australia (CHC) welcomes the opportunity to provide comment on the Therapeutic Goods Administration's "Guidance on Release for Supply for Medicines Manufacturers," version 1.0, June 2013.

The CHC is the peak industry body representing companies involved in all facets of the complementary medicine industry from: sponsors, manufacturers, importers, exporters, raw material suppliers, wholesalers, distributors and retailers. The CHC is committed to a high growth and sustainable complementary medicines industry. We promote industry advancement, whilst ensuring consumers have access to complementary medicines of the highest quality, contributing to improved population health outcomes.

The CHC notes the TGA's "Guidance on Release for Supply for Medicines Manufacturers" document intends to address:

- the general requirements and responsibilities regarding Release for Supply (RFS) by an Authorised Person (AP) applicable to all TGA licensed and/or certified manufacturers and to Australian sponsors
- specific considerations on how these general requirements and responsibilities can be met for specific areas of manufacture, for example complementary medicines manufacturing supply chains.

General Comments

1. The "Guidance on Release for Supply for Medicines Manufacturers" commenced following concerns expressed by industry based on past experience with the implementation of the PIC/S Code currently in force in Australia (PE 009-8-15 January 2009). This version of the Code was adopted in 2009 without any prior consultation with industry. As such it introduced requirements for Product Quality Reviews (PQRs) and Ongoing Stability program steps to be considered by an Authorised Person (AP) prior to the release for supply of a batch. As a result of confusion surrounding the responsibilities of the AP, the TGA set up an *ad hoc technical working group* to produce further guidance for complementary medicine specific issues. The TGA's Technical Working Group on Complementary Medicines has since generated a suite of interpretative guidance documents to work to, as described below:

    - On-going Stability Testing for Listed complementary medicines
    - Product Quality Review for Listed complementary medicines
    - Process Validation for Listed complementary medicines
    - Supplier qualification
    - Sampling and testing of complementary medicines
    - Guidance on Release for Supply for medicine manufacturers (under development).

2. The CHC, along with other stakeholders, raised concerns with regard to the level of responsibility that this placed upon the AP and the difficulty APs were having in determining

the level of detail and supporting documents that was expected to be held relating to PQRs and Ongoing Stability for complementary medicines. We note, with some concern, that 4 years has now passed since the current Code was adopted and Part 1 on Release for Supply has only now been released for comment, while no version is yet available for additional sections of this document.

3. Our members continue to express concern, in particular contract manufacturers, continue to wrestle with producing or obtaining Product Quality Reviews as a shared responsibility between them and the sponsor. The adoption of PE 009-8 has led to a number of sponsors now viewing the preparation of PQRs as solely a GMP responsibility and or a responsibility of the Licensed Manufacturer. This has lead to a situation where many in industry now believe that there is too great responsibility being placed on the licensed manufacturer and the APs that release batches.

    1. The CHC notes that there is currently no mechanism available to the TGA to audit or inspect sponsors who are not licensed manufacturers and that the concept of licensing of sponsors has been previously canvassed with industry by the OMQ. The CHC submits that the licensing of sponsors be considered and canvassed once again.

4. It is important to note that the PIC/S Guide, being based on the European Medicines Agency (EMA) Code, is in the main written to cover prescription and over-the-counter (OTC) medicines in Europe. A seemingly minor change can have significant impact in the Australian regulatory environment, most notably for complementary medicines. The majority of prescription medicines for example, contain a single active while OTC medicines rarely contain more than four active ingredients, which makes the preparation of PQRs and establishment of an Ongoing Stability program far more straightforward than for complementary medicines where it is common place to have 20 to 30 active ingredients. In addition, many contract manufacturers may only make a small number of batches a year of a specific product, and often for a range of similar products. While we note that there are some concessions with grouping products for PQRs and Ongoing Stability in current guidance documents, this is often very difficult in practice with the time taken in providing justifications for grouping, often negating any gains made.

The terminology issue identified below, while applicable to all therapeutic goods, refers only to the application of the draft guidance document to complementary medicines.

<u>Terminology</u>

1. the glossary defines “Release for Supply” as is it used throughout the draft guidance document. This definition includes b) the “Release for further processing (of an intermediate or bulk product) to the next step in manufacture”.
2. The term “Supply” is defined in section 3 of the *Therapeutic Goods Act 1989* (the Act) as:

    i. supply by way of sale, exchange, gift, lease, loan, hire or hire-purchase; and

ii. supply, whether free of charge or otherwise, by way of sample or advertisement; and

iii. supply, whether free of charge or otherwise, in the course of testing the safety or efficacy of therapeutic goods in persons; and

iv. supply by way of administration to, or application in the treatment of, a person.

The CHC notes that "Supply" has "by way of administration to, or the application in the treatment of, a person" as a required part of its definition. Consequently, when a product is "Released for Supply" it is a "Release" for "by way of administration to, or the application in the treatment of, a person" of that product. Such an understanding is consistent with the RFS activity being the last step in manufacture of the product.

3. The other steps in manufacture occur before the RFS step. These other steps do not involve any aspects of "Supply" as defined above. For example, product packed in bulk is not "Supplied" for "the administration to, or the application in the treatment of, a person" of that bulk product. Rather it needs to be released to the next step in manufacture, typically conversion to a market pack. Therefore, any approval of any of those other steps in manufacture to enable the product to be involved in the next step in manufacture should not be called a "Release for Supply" rather a "Release from Manufacture" (RFM). Since the introduction of the Therapeutic Goods Act over 20 years ago, manufacturers of therapeutic goods have used a RFM certification to enable in-process product to move to the next step in manufacture. It is submitted that only the last step in manufacture will require a RFS certification and the other, earlier steps in manufacture will require a RFM certification.

   The CHC agrees with Clause 1.2 of the consultation draft that "Release for Supply" is considered a step in manufacture, however does not agree with the implications in the rest of the consultation document that all earlier steps in manufacture (as defined in this clause) can also be considered to be steps of "supply", rather they are steps in manufacture.

4. The AP doing the RFS step in manufacture, will need to have access to the RFM certificates relating to all the earlier steps in manufacture without the need to have access to all the documentation that was used to generate the RFM certification.

Specific Comments

5. The majority of complementary medicines supplied in Australia are manufactured using more than one GMP licensed and/or certified site. GMP compliant completion of these different steps in manufacture at these different sites is certified by the AP at that site. That certification is then provided to the AP at the site next in the manufacturing chain.

6. Clause 1.4: As the level of education and expertise of the AP conducting any Release activity is verified by the TGA during inspections, it would be sufficient and adequate for the names of the TGA verified AP(s) who will conduct the RFM activity for each relevant, non- RFS manufacturing steps, to be included in the GMP agreement covering manufacture of the product. If so, all the APs doing RFS step in manufacture will have to do, is to check that the correct name of the AP is on the relevant RFM certification.

   The CHC highlights, that the consultation paper does not address or acknowledge the issue that the AP at the contracted manufacturing step of packing will also do the RFS step in manufacture. Whilst this AP must have the relevant verified level of education and expertise relevant to packing, that AP may not have the relevant verified level of education and expertise relevant to all the earlier steps in manufacture. The AP doing the RFS step will rely on the relevant verified level of education and expertise of the APs at the earlier steps in manufacture when the final AP conducts the RFS step.

7. Clause 1.6: It is agreed that the terms
    1. "Release for Sale" is an obsolete term; and
    2. "Release for Supply" applies to the release:
        i. of a finished batch for supply to the Australian market;
        ii. of a Phase 2 or later investigational medicinal product for use in human clinical studies;
        iii. for export.

8. Clause 1.6.b: As discussed and explained above, it is disagreed that the term "Release for Supply" applies to the "Release of an Active Pharmaceutical Ingredient (API) or an intermediate or bulk product for further processing to the next manufacturer in the manufacturing supply chain". The word "supply" is being used with two different meanings and contexts in the last explanatory sentence.

9. Clause 1.7: This clause considers a major issue of sharing information that is problematic within the manufacture of complementary medicines.
    1. The products made under contract for one sponsor may be part of a group of similar products
        i. Made at that manufacturer(s) for other sponsors
        ii. Contracted out by the sponsor to different manufacturers.

       The two suggested options to resolve the confidentiality problems are however not commonly acceptable to manufacturers or sponsors.

    2. Such grouping requires information to be collected for Product Quality Reviews (PQR). There are confidentiality concerns about the application of data for index (or chosen) products within a group at a manufacturer being used for or being supplied by that manufacturer to either another manufacturer later in the manufacturing chain or to Sponsors who are not the Sponsor of the index product. These concerns have resulted in costly and time consuming sponsor manufacturer specific PQR data being provided to APs. This problem impinges on the RFS activity, however is better considered as part of the PQR review.

10. Clause 2.1d: The AP doing the RFS step has to ensure that;
    1. "the principle manufacturing and release testing processes (as per the finished product specifications) have been validated." However, this is causing confusion about how the proof of such validation and its adequacy is conveyed to the AP doing the RFS step. It would seem reasonable that the AP has to be satisfied without requiring innumerable folders of validation documentation to be sent to that AP. It will require a measure of goodwill and a realistic approach on behalf of that AP, the Sponsor and all manufacturers and testers. The CHC submits that appropriate wording be included in the RFM statement for the relevant step in manufacture and that TGA inspectors at the site doing the RFS step accept such wording as being sufficient and adequate. TGA inspectors at the relevant manufacturing site can verify the sufficiency and adequacy of the wording.

    2. "account has been taken for the actual production conditions, manufacturing the test records." The same type of problem as with the validation occurs here to. Again, the CHC suggests that appropriate wording be included in the RFM statement for the relevant step in manufacture and that TGA inspectors at the site doing the RFS step accept such wording as being sufficient and adequate. TGA inspectors at the relevant manufacturing site can verify the sufficiency and adequacy of the wording.

11. Clause 2.1.h: The AP doing the RFS step has to ensure that "All internal audits and supplier audits have been carried out as required by the quality management system (presumably at the relevant manufacturing site and not necessarily at the site undertaking the RFS step)." The same type of problem as seen with validation can be seen here. Again, it is suggested that appropriate wording be included in the RFM statement for the relevant step in manufacture and that TGA inspectors at the site doing the RFS step accept such wording as being sufficient and adequate. TGA inspectors at the relevant manufacturing site can verify the sufficiency and adequacy of the wording.

12. Clause 2.4.a: The AP doing the RFS step has to "ensure that the PQR is performed in a timely manner and is accurate, as outlined in GMP clause 1.4". This is done "by either the AP being involved in the preparation of the PQR or has the full results available".

    1. For PQR activities for complementary medicines contract manufactured and supplied in Australia, it is now common for the Sponsor to arrange for each of the manufacturing sites to supply the sponsor with a summary report relating to the relevant PQR activities at that manufacturing site. Along with the PQR activities at the Sponsor, these summary reports are then sent by the Sponsor to the AP doing the RFS step in manufacture. However, the new requirement that "Full results need to be available" means that again innumerable folders of PQR documentation would be required to be sent to the Sponsor.

       The CHC submits that the current summary reports continue to be sent to the sponsor and that TGA inspectors at the site doing the RFS step accept such summary reports as being sufficient and adequate. TGA inspectors at the site that prepares

the summary report verify that the summary reports are sufficient and adequate (as inferred by clauses 5.4 and 5.5 of the draft consultation document.

13. Clause 2.4b. The AP doing the RFS step has to "monitor product stability in an on-going stability program as outlined in GMP clauses 6.23-6.33." This is done "by either the AP being involved in the preparation of the on-going stability program or has full results available." These clauses within the Code of GMP clearly distinguish on-going stability programs from internal long term stability programs. The CHC highlight that listed complementary medicines supplied in Australia can obtain a Market Authorisation without submitting any initial long term stability data to TGA for evaluation, however do have to be able to justify the applied shelf life and to commit to obtaining data to substantiate that shelf life. Therefore, the AP doing the RFS activity is not required to consider the data being generated to substantiate the applied shelf life since that is part of the initial long term stability program.

    1. It is possible that the AP doing the RFS activity may wish to review the substantiation document for the applied shelf life. However, once the product has data to substantiate the applied shelf life, it will then be entered into an ongoing stability program and that data from that on-going stability program will be subject to review by the AP doing the RFS step in manufacture.
       This review is subject to the same type of problem as the validation issue above and it is suggested that the current ongoing stability summary reports continue to be sent to the sponsor and that TGA inspectors at the site doing the RFS step accept such summary reports as being sufficient and adequate.

    2. It is further noted that a grouped stability program for ongoing stability studies may include products other than those that the AP has been engaged to release. Access to this data by the AP may then be seen to breach commercial confidence. It should be sufficient that a summary report be acceptable as evidence of substantiation of the assigned expiry, where the data is managed and reviewed by a party holding a licence to manufacture. The full data will then be able to be made available to a TGA inspector at inspection of either the site performing RFS (by request and transfer to the inspector) or at the site holding the data.

14. Clause 3.3: The AP performing the release for supply of the finished product batch is allowed to rely in part on decisions of one or more other APs. The term "in part" needs to be further clarified, particularly in reference to 2.3 above.

15. Clause 3.4.a: it is submitted that the GMP agreement should define the RFM (not RFS) activity for each "partial" manufacturer within the chain of manufacture.

16. Clause 3.4.d: it is submitted that the decision to approve the RFM (not RFS) activity for each "partial" manufacturer within the chain of manufacture should be recorded through a legally valid signature.

17. Clause 3.4.e: it is unpractical to expect the AP conducting the RFS step in manufacture to conduct supplier audits on each manufacturer involved. The CHC submits that if any manufacturer is licensed or certified by TGA to conduct the particular steps in manufacture, that this TGA approval should be sufficient and adequate.

18. Clause 4.3: it is unlikely that a contract packer that does the RFS step in manufacture will want to be involved in the Compliance Verification (CV) of an overseas manufacturer of bulk product. Such CV will be done by the Sponsor and the outcome summarised to the AP doing the RFS step in manufacture.

While the draft "Guidance on Release for Supply for Medicines Manufacturers" document attempts to address some of the issues mentioned above, the CHC submits that major concerns surrounding the level of responsibility placed on to the AP have not been fully addressed. While the guidance does provide more detail around what documents an AP performing Release for Supply is expected to review, the fundamental question as to whether the AP or Sponsor should be expected to bear this level of responsibility remains.