CHC Submission to the Therapeutic Goods Administration on the Proposal for automatic adoption of new versions of the PIC/S Guide to Good Manufacturing Practice for Medicinal Products

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Introduction

The Complementary Healthcare Council of Australia (CHC) thanks you for the opportunity to provide comment on the Therapeutic Goods Administration's proposal for 'rolling' automatic adoption of new versions of the PIC/S Guide to Good Manufacturing Practice for Medicinal Products (PIC/S GMP). We note the proposal is in combination with an improved industry consultation process on future revisions and is to include a transition period of 6 months from the date of publication by PIC/S.

The CHC is the peak industry body representing companies involved in the manufacture and distribution of complementary medicines. We are unique in representing the entire supply chain from: manufacturers, importers, exporters, raw material suppliers, wholesalers, distributors and retailers. The CHC are 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.

We are pleased to enclose to this submission comments in reference to:

1. The proposal for rolling adoption of new versions of the PIC/S Guide to Good Manufacturing Practice for Medicinal Products; and
2. The Update from PIC/S Guide for GMP for medicinal products – PE 009-8 - 15 January 2009 to PIC/S Guide for GMP for medicinal products – PE 009-10 - 1 January 2013.

1. Response to the proposal for rolling adoption of new versions of the PIC/S Guide

The CHC thanks the Office of Manufacturing Quality (OMQ) for the provision of a comparison document between the 2009 and 2013 editions of the PIC/S Guide to Good Manufacturing Practice (GMP) in facilitating a meaningful response to this consultation. The CHC acknowledges the undertaking of the TGA and Medsafe in having negotiated for the opportunity for Australia and New Zealand to comment on the amended draft PIC/S Guide and for that comment to be considered before the amendment is adopted by PIC/S. We note the proposal intends to provide for the opportunity for consultation with industry on the adoption of each amendment before it becomes a Code of GMP in Australia. However, the CHC can not support the proposal for a rolling adoption of new versions of the PIC/S Guide to GMP, for the reasons outlined in this submission.

The CHC is greatly concerned that the proposal for 'rolling adoption' and the proposed additions to Annex 7: Herbal Medicinal Products will pose significant challenges and negatively impact the manufacture of complementary medicines in Australia. This is due to the fact that complementary medicines, particularly listed complementary medicines, are not regulated as 'medicines' in other countries. As such the GMP requirements under the PIC/S framework creates an unequitable situation in global trade markets.

Obtaining and maintaining GMP for products being imported into these markets and the ongoing incremental increases in standards such as Herbal Medicinal Products is resulting in an unworkable

barrier for this highly valued industry. A consideration of the regulations of complementary medicines should also reflect a balance that ensures the continuity and reasonable cost of supply of these medicines to the end-user and ultimately the consumer.

In particular, the CHC is concerned with this proposal based on past experience with the implementation of the PIC/S code in 2009 (PE 009-8 - 15 January 2009). This version of the code was adopted 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. The CHC, along with other stakeholders, raised concerns with regard to the level of responsibility that this placed on 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. These concerns still remain and have lead to even greater concerns being expressed by the industry on the changes being proposed.

The CHC is also concerned that comments made by the industry in Australia and/or by the TGA, may be rejected or not incorporated into a new version of the PIC/S Guide and seeks clarification of what the position will be if this occurs. Will Australia still proceed to adopt a new version of the PIC/S Guide under a rolling adoption process if comments made by Australia are rejected or deferred?

The difficulty in positioning complementary medicines into model intended for pharmaceutical medicines can be demonstrated most efficiently in the need for the TGA's Technical Working Group on Complementary Medicines (TWG-CM) to generate a suite of interpretative guidance documents to work to by exception; 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).

During previous updates to the PIC/S Guide, the TGA and industry have worked collaboratively to generate these interpretive guidance documents detailing an acceptable approach for complementary medicines to meet the requirements with a level of confidence. The proposal for a rolling automatic adoption of PIC/S will not, in CHC's view, change the current circumstance where an interpretive guide will need to be generated for specific application within the Australian regulatory environment.

A fixed 6 month transition period is proposed after PIC/S publication. Given the time it has taken on average to generate guidance material and to conduct information sessions with industry, where required, such a fixed transition period does not seem feasible. While we applaud the TGA in setting up the technical working groups, we note with some concern that 4 years has now passed since the 2009 PIC/S Code was adopted and the release for supply guidance document is still under development. The CHC therefore can not support such a fixed transition time and proposes a

minimum 12 month transition time with the flexibility to notify of the need for an extension, where complex documentation is required.

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.

Our members continue to express concern, in particular contract manufacturers continue to grapple with producing or obtaining Product Quality Reviews as a shared responsibility between them and the sponsor. The adoption of PE 009-8 has lead 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. The CHC suggests that licensing of sponsors should be considered and canvassed once again to clarify and underpin sponsors obligations.

The CHC believes a system of automatic adoption of PIC/S GMP requirements will continually place industry on the back foot, developing appropriate guidance material to take precedence over the GMP requirements for application in the Australian regulatory environment. Such a framework is not sustainable for the complementary medicines industry. The CHC advocates for a more viable option, one where complementary medicine specific International Standards/Code of GMP are developed for the manufacture of these medicines accompanied by complementary medicine-relevant legislation. The overarching goal should be to provide for more effective, efficient and less burdensome regulatory oversight of the quality management systems of complementary medicine manufacturers.

PIC/S Guide to Good Manufacturing Practice for Medicinal Products, PE 009-10, Part 1

PE 009-10	Concerns identified	Proposal
4.27 Written release and rejection procedures should be available for materials and products, and in particular for the certification for sale of the finished product by the Authorised Person(s). All records should be available to the Authorised Person. A system should be in place to indicate special observations and any changes to critical data	While the nature of this change is described as providing a 'closer reference for supply activities', there are complexities with release for supply where more than one party is involved in the steps of manufacturer. This can be seen in the generation of the release for supply technical guidance document (still under development).	A variety of these situations should be addressed in the release for supply guidance document.

PIC/S Guide to Good Manufacturing Practice for Medicinal Products, PE 009-10, Annexes

Annex 3: Radiopharmaceuticals – the CHC makes no comment to this Annex

Annex 6: Medicinal gases – the CHC makes no comment to this Annex

Annex 7: Herbal Medicinal Products

Annex 7: Herbal Medicinal Products	Concerns identified	Proposal
Because of their often complex and variable nature, control of starting materials, storage and processing assume particular importance in the manufacture of herbal medicinal products.		The CHC is greatly concerned that the proposal for additions to Annex 7: Herbal Medicinal Products

Annex 7: Herbal Medicinal Products	Concerns identified	Proposal
The "starting material" in the manufacture of an herbal medicinal product[1] can be a medicinal plant, an herbal substance[2] or an herbal preparation[1]. The herbal substance should be of suitable quality and supporting data should be provided to the manufacturer of the herbal preparation/herbal medicinal product. Ensuring consistent quality of the herbal substance may require more detailed information on its agricultural production. The selection of seeds, cultivation and harvesting conditions represent important aspects of the quality of the herbal substance and can influence the consistency of the finished product. Recommendations on an appropriate quality assurance system for good agricultural and collection practice are provided in national or international guidance documents on Good Agricultural and Collection Practice for starting materials of herbal origin[3]. This Annex applies to all herbal starting materials: medicinal plants, herbal substances or herbal preparations. **Table illustrating the application of Good Practices to the manufacture of herbal medicinal products[4]** **Explanatory Notes** †..The GMP classification of the herbal material is dependent upon the use made of it by the manufacturing authorisation holder. The material may be classified as an active substance, an	- It should be noted that most herbal raw materials come from wild collection / wild crafted and are not necessarily a product of agriculture per se.	will pose significant challenges and negatively impact the manufacturer of complementary medicines in Australia. What may be considered a minor change to aspects of revisions of PIC/S, may in fact pose significant changes for the industry. For example, increased requirements for herbal starting material as detailed in clause 8 below.

[1] Throughout the annex and unless otherwise specified, the term "herbal medicinal product / preparation" includes "traditional herbal medicinal product / preparation".
[2] The terms herbal substance and herbal preparation are considered to be equivalent to the terms herbal drug and herbal drug preparation respectively.
[3] European Medicines Agency (EMA), World Health Organization (WHO) or equivalent.
[4] This table expands in detail the herbal section of Table 1 in Part II of the GMP Guide.
EMA, WHO or equivalent

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intermediate or a finished product. It is the responsibility of the manufacturer of the medicinal product to ensure that the appropriate GMP classification is applied. * Manufacturers should ensure that these steps are carried out in accordance with the marketing authorisation / registration. For those initial steps that take place in the field, as justified in the marketing authorisation / registration, the national or international standards of Good Agricultural and Collection Practice for starting materials of herbal origin (GACP)# are applicable. GMP is applicable to further cutting and drying steps. ** Regarding the expression from plants and distillation, if it is necessary for these activities to be an integral part of harvesting to maintain the quality of the product within the approved specifications, it is acceptable that they are performed in the field, provided that the cultivation is in compliance with national or international standards of GACP#. These circumstances should be regarded as exceptional and justified in the relevant marketing authorisation / registration documentation. For activities carried out in the field, appropriate documentation, control, and validation according to the GMP principles should be assured. Regulatory authorities may carry out GMP inspections of these activities in order to assess compliance.		
1. Herbal substances should be stored in separate areas. The storage area should be equipped in such a way as to give protection against the entry of insects or other animals, especially rodents. Effective measures should be taken to prevent the spread of any such animals and micro-		

Annex 7: Herbal Medicinal Products	Concerns identified	Proposal
organisms brought in with the crude substance, to prevent fermentation or mould growth and to prevent cross-contamination. Different enclosed areas should be used to quarantine incoming herbal substances and for the approved herbal substances. The storage area should be well aerated and the containers should be located in such a way as to allow free circulation of air. Special attention should be paid to the cleanliness and good maintenance of the storage areas particularly when dust is generated. Storage of herbal substances and herbal preparations may require special conditions of humidity, temperature or light protection; these conditions should be provided and monitored.		
5. Specific provisions should be made during sampling, weighing, mixing and processing operations of herbal substances and herbal preparations whenever dust is generated, to facilitate cleaning and to avoid cross-contamination, as for example, dust extraction, dedicated premises, etc.	No concerns identified.	
6 The equipment, filtering materials etc. used in the manufacturing process must be compatible with the extraction solvent, in order to prevent any release or undesirable absorption of substance that could affect the product.	New clause.	
7. Herbal medicinal product manufacturers must ensure that they use only herbal starting materials manufactured in accordance with GMP and the Marketing Authorisation dossier. Comprehensive documentation on audits of the herbal starting material suppliers carried out by, or on behalf of the herbal	The CHC notes that clause 7 is a new requirement that does however seek to adopt an already existing informal reference document - Good Agricultural and Collection Practice (GACP). It adopts	

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medicinal product manufacturer should be made available. Audit trails for the active substance are fundamental to the quality of the starting material. The manufacturer should verify, where appropriate, whether the suppliers of the herbal substance / preparation are in compliance with Good Agricultural and Collection Practice and – if not – apply appropriate controls in line with Quality Risk Management (QRM). 8. To fulfil the specification requirements described in the basic requirements of the Guide (Chapter 4), documentation for herbal substances / preparations should include: the binomial scientific name of plant (genus, species, subspecies / variety and author (e.g. Linnaeus); other relevant information such as the cultivar name and the chemotype should also be provided, as appropriate; details of the source of the plant (country or region of origin and where applicable, cultivation, time of harvesting, collection procedures, possible pesticides used, possible radioactive contamination, etc.); which part(s) of the plant is/are used; when a dried plant is used, the drying system should be specified; a description of the herbal substance and its macro and microscopic examination; suitable identification tests including, where appropriate, identification tests for constituents with known therapeutic activity, or markers. Specific distinctive tests	GACP more formally but still allows for Quality Risk Management (QRM) if this cannot be met. Feedback from members has been that in practice these requirements have not been very achievable. The CHC questions how 'appropriate controls' will be interpreted? The CHC notes the allowance of QRM especially as many herbal starting materials used in Australia are wild crafted. - Is there to be a separate list and	

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are required where an herbal substance is liable to be adulterated / substituted. A reference authentic specimen should be available for identification purposes; the water content for herbal substances, determined in accordance with the relevant Pharmacopoeia; assay of constituents of known therapeutic activity or, where appropriate, of markers; the methods suitable to determine possible pesticide contamination and limits accepted in accordance with relevant Pharmacopoeia methods or, in absence of thereof, with an appropriate validated method, unless otherwise justified; tests to determine fungal and/or microbial contamination, including aflatoxins, other mycotoxins, pest-infestations and limits accepted, as appropriate; tests for toxic metals and for likely contaminants and adulterants, as appropriate; tests for foreign materials, as appropriate; any other additional test according to the relevant Pharmacopoeia general monograph on herbal substances or to the specific monograph of the herbal substance, as appropriate. Any treatment used to reduce fungal/microbial contamination or other infestation should be documented. Specifications and procedures should be available and should include details of process, tests and limits for residues.	criteria for determining what herbal substances are considered liable to be adulterated/substituted? - Is additional guidance required here?	Additional guidance be considered.

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9. The processing instructions should describe the different operations carried out upon the herbal substance such as cleaning, drying, crushing and sifting, and include drying time and temperatures, and methods used to control cut size or particle size. 10. In particular, there should be written instructions and records, which ensure that each container of herbal substance is carefully examined to detect any adulteration/substitution or presence of foreign matter, such as metal or glass pieces, animal parts or excrement, stones, sand, etc., or rot and signs of decay. 11. The processing instructions should also describe security sieving or other methods of removing foreign materials and appropriate procedures for cleaning/selection of plant material before the storage of the approved herbal substance or before the start of manufacturing. 12. For the production of an herbal preparation, instructions should include details of solvent, time and temperatures of extraction, details of any concentration stages and methods used.		
13. Due to the fact that medicinal plant/herbal substances are heterogeneous in nature, their sampling should be carried out with special care by personnel with particular expertise. Each batch should be identified by its own documentation. 14. A reference sample of the plant material is necessary, especially in those cases where the herbal substance is not described in the relevant Pharmacopoeia. Samples of unmilled plant material are required if powders are used. 15. Quality Control personnel should have particular expertise and experience in herbal substances, herbal preparations and/or herbal medicinal products in order to be able to carry out	- This clause is new however, the requirements to keep reference samples was already effective based on Annex 19. Industry typically has sourced reference samples from local herbariums as difficulties have been reported	

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identification tests and recognise adulteration, the presence of fungal growth, infestations, non-uniformity within a delivery of crude material, etc. 16. The identity and quality of herbal substances, herbal preparations and herbal medicinal products should be determined in accordance with the relevant current national or international guidance on quality and specifications of herbal medicinal products and traditional herbal medicinal products and, where relevant, to specific pharmacopoeial monographs	with obtaining these samples from overseas and at the point of control at the Australian boarder.	

Annex 11: Computerised systems - the CHC makes no comment to this Annex.
Annex 13: Investigational medicinal products - the CHC makes no comment to this Annex.