Complementary Medicines Australia submission to the Therapeutic Goods Administration Consultation:

Annotation of the European Union Guidelines in respect of traditional medicines

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Complementary Medicines

Complementary Medicines Australia is the leading voice and industry body for manufacturers, raw material suppliers, distributors, consultants, retailers, allied health professionals and educators. CMA members represent over 70% of all product sales and the full value chain in Australia. As the principal reference point for members, the government, the media and consumers, CMA communicate on broad issues relating to the industry.

The complementary medicines sector is well-established, having evolved over the last 30 years to become a world-class industry that supports research, employment and high-skilled advanced manufacturing. High demand for complementary medicine products is driving steady growth, with the industry reaching $5.2 billion in revenues in 2018. Over the last five years, the sector has achieved $2 billion in growth, predominantly as a result of strong exports. Australian brands are recognised and trusted internationally, with China importing more complementary medicines from Australia than anywhere else in the world.

The increasing consumer demand for complementary medicines has resulted in the industry becoming a significant pillar in preventative healthcare, both economically and as an employer. Over the last few decades the medicines sector has evolved into a major world-class industry supporting domestic jobs, research, manufacturing and exports.

Consultation

Complementary Medicines Australia (CMA) welcomes the opportunity to provide comment on the TGA's consultation on adoption of the EU guidelines in Australia for medicines.

Specifically our submission is in regards to the following proposal:

- EMA/HMPC/104613/2005 Rev. 1 (pdf,171kb)
  Assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products

  Annotation: **The TGA does not consider this guideline to be applicable to complementary medicine applications seeking indications based on established tradition of use. In Australia, an established tradition of use is considered to be three generations of human use, equating to approximately 75 years.**

- EMEA/HMPC/166326/05(pdf,155kb)
  Clinical assessment of fixed combinations of herbal substances/herbal preparations

  Annotation: **The TGA does not consider this guideline to be applicable to complementary medicine applications seeking indications based on established tradition of use. In Australia, an established tradition of use is considered to be three generations of human use, equating to approximately 75 years.**

Summary Position

There are two EU Guidelines relevant to the complementary medicines sector referenced: EMA/HMPC/104613/2005 Rev. 1 and EMEA/HMPC/166326/2005 with the caveat, that these specific guidelines are not relevant to complementary medicines based on the definition of traditional use:

> *"Annotation:* The TGA does not consider this guideline to be applicable to complementary medicine applications seeking indications based on established tradition of use. In Australia, an established tradition of use is considered to be three generations of human use, equating to approximately 75 years."

Complementary Medicines Australia has consulted industry members and experts to assess the proposal and subsequently submit that:

1) The guidance materials are relevant to the Australian context, and therefore that **the proposed annotations must not be adopted:**

   - Remaining consistent with the TGA's international engagement and harmonisation strategy with comparable regulatory authorities;
   - Meets Government goals regarding the de-regulation agenda of the current Government including the Terms of Reference of the Deregulation Taskforce by the Department of Treasury;
   - Remains consistent with the recommendations set out by the Medicines and Medical Devices Regulation (MMDR) Expert Panel Review;
   - Would improve competitiveness of the Australian complementary medicine sector in an international marketplace;
   - Adoption of the annotation would place Australian complementary medicines – both substances and products - at a significant disadvantage relative to Europe, representing an approximately 45 year delay in Australian products relative to Europe, an unnecessary and harmful policy in an increasingly global commerce environment; and
   - Non-adoption of the annotation poses no threat to public health and safety as the EMA is established as a notably safe regulator; the products and substances are low risk in nature; further, substances approve for use in Australia as complementary medicines must undergo additional specific safety and quality evaluation before market supply. The evidence consideration is also of little relevance within a globally harmonised context.

2) The three generation/75-year rule relating to an established tradition of use is of arbitrary origin and questionable relevance in the face of respected and authoritative international regulators. The rule is not legislative but was originally implemented as a general guiding principle. It **must be reviewed with the view of discarding this principle** in favour of alignment with international comparable regulatory authorities, particularly Europe and Canada. This is congruent with the current TGA activities of reviewing the Evidence Guidelines for Listed medicines, and the de-regulatory measures referred to by both MMDR reforms and the Government's Deregulation Taskforce.

Background and Scope

Background to EU guidelines in Australia:

As stated on the TGA website, 'while EU and ICH technical Guidelines adopted in Australia are generally not mandated in Australian legislation they provide guidance to sponsors to assist them to meet the legislative requirements…' (https://www.tga.gov.au/publication/scientific-guidelines).

The 26BB permissible ingredients determination is not used to specify requirements to comply with EU Guidelines per se. Specific requirements that are outlined in scientific guidelines may be included in the 26BB list at a future date, where the requirements are considered necessary to maintain the quality and/or safety of an ingredient.

Our guidance material (eg. Australian regulatory guidelines for complementary medicines (ARGCM)) advises that sponsors should refer to certain guidelines to assist them to meet their legislative requirements, with regard to quality and safety for example.

For registered medicines (including complementary), under paragraph 25(1) the Act the delegate is required, when evaluating an application for registration, to consider:

'...whether the quality, safety, and efficacy of the goods for the purposes for which [the goods] are to be used have been satisfactorily established.'

Australia-specific guidelines and adopted EU and ICH guidelines describe the kind of data and information to be included in each Module of a dossier to demonstrate quality, safety, and efficacy. If the dossier does not contain all of this information, the TGA may not be able to determine whether the quality, safety and efficacy of the medicine has been satisfactorily established. See https://www.tga.gov.au/book-page/mandatory-requirements-1 for more information (scroll down to subsection Australia-specific and adopted European Union and ICH guidelines).

Scope of feedback within this submission

The EMA documents provide guidance on the types of indications and what can be claimed. With the Permissible Indications Determination and other specific guidance for Listed (Assessed) medicines applicable in Australia, CMA will not comment on these details. Both EMA guidelines draw distinction between 'well-established use" and "traditional use". CMA will limit its commentary to those matters related to traditional medicines.

Consultation method and impact upon various CM application types

The consultation does not clarify the scope or effect of the annotation upon the different application types for complementary medicines.

CMA are concerned that, unlike other EU guideline adoptions which are for a straight-forward adoption, the relevance and impact of the proposed annotations to the complementary medicine industry have complex interrelation with complementary medicine regulation which have not not been adequately described in the consultation. Consequently, CMA are concerned that industry stakeholders have not

been fair and adequate opportunity to assess the potential meaning, impacts and effect of the proposal upon complementary medicine applications of all types and categories.

The effect described below is the presumed effect upon various complementary medicine application types. We welcome further specificity on the intended effect and additional downstream effects of further adoption into other documents, if relevant.

1) Impact of Adopting the Annotation for New CM Substance Applications

In order to be assessed as a new substance application for complementary medicines, a substance must be a complementary medicine (Therapeutic Goods Regulations 1990):

> ***RCM1 application*** means an application made under section 23 of the Act to register a **complementary medicine**
>
> ***complementary medicine*** means a therapeutic good consisting wholly or principally of 1 or more designated active ingredients, each of which has a clearly established identity and **a traditional use**.
>
> ***traditional use***, for a designated active ingredient, means use of the designated active ingredient that:
> (a) is well documented, or otherwise established, according to the accumulated experience of many traditional health care practitioners over an extended period of time; and
> (b) accords with well-established procedures of preparation, application and dosage.

The 3 generation/75 year rule is not legislative, and CMA oppose it becoming so, considering that's its inclusion appears to be an arbitrary agreement for general guidance purposes at the time due to the absence of other guidance or international harmonisation at the time of its inception.

In respect of new substance applications, the definition of traditional use must be aligned in policy with international regulators, thus, the annotation must not adopted. Adoption of the annotation will mean that new substances which have a tradition of use in Europe that align with the EU guidelines will not be assessable as in ingredient available for use in Listed or Listed (Assessed) Medicines in Australia until the full 75 years has passed.

This will result in Australia lagging behind global competitors by up to 5 decades for many substances to even gain market entry, without a justifiable reason, which is unacceptable from a Government red-tape and de-regulatory perspective particularly as health and safety will not be impacted.

2) Impact of Adopting the Annotation for Listed Medicines (evidence assessments)

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 it is our understanding that 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.

Despite this, it is apparent that the adoption of the annotation will also result in the adoption of this policy into the Evidence Guidelines for Listed Medicines, and that certain high quality sources of traditional evidence for complementary medicines such as the EMA monographs or Health Canada monographs will become unavailable for use by Listed medicine sponsors. In a rapidly increasing global

commerce environment, this would constitute a grossly unreasonable regulatory barrier for Australian businesses relative to international dietary supplement companies, many of whom do not adhere to the same high standards of GMP and quality standards for both substances and finished products which Australian medicines are required to comply with.

3) Impact of Adopting the Annotation for Listed (Assessed) or Registered Complementary Medicines

Whilst the impact for these medicines is expected to be lower as the key indication is based on scientific evidence, there are other traditional evidence indications that may be considered in applications. The expected impact on these medicines would be the same for:

> Item 1) in respect of Listed (Assessed) Medicines, as important and globally relevant substances would not be available for this category of goods;
>
> Item 2) in respect of applications that include traditional indications.

International engagement and harmonisation

Alignment with EMA guidance materials (non-adoption of the annotation) is in keeping with:

- The third key goal of the TGA international Engagement Strategy 2016 – 2020 objective: "participation in work sharing and convergence of activities".
- In considering the case for regulatory reform, the MMDR Expert Panel commented on the benefits of harmonising international regulatory frameworks, noting that there are benefits for consumers and efficiencies for industry from greater harmonisation. The Panel concluded that allowing for greater flexibility in approval pathways for medicines and medical devices, including greater use of overseas assessment reports and provisional approvals, would expedite access to market without compromising the safety, quality and efficacy or performance. Numerous MMDR recommendations in respect of complementary medicines go on to recommend the utilisation of reports by comparable overseas regulators, of which the EMA is one of the most notable. The Government accepted the recommendations. The introduction of the annotation is against the spirit of the MMDR reforms and recommendations, despite the 75 year guiding only being an approximation developed very early in the days of complementary medicine evidence reviews in Australia. The 75-year guidance does not have any meaningful origin, basis, or international recognition and should be viewed as such within the wider regulatory content.
- Maintaining harmony with international initiatives on traditional medicines, including the World Health Organisation's Traditional Medicine Strategy 2014-2023, and the IRCH – International Regulatory Cooperation for Herbal Medicines.

One such activity has been the adoption of guidelines published by equivalent or comparable overseas regulators to increase business efficiencies by reducing duplication of effort.

CMA notes that the Australian regulatory environment for listed complementary medicines, is not based on a monograph system such as that of the EMA, however EMA guidelines are already considered adequate substantiating evidence for listed complementary medicines and may also constitute

supporting evidence in Listed Assessed, Registered complementary medicine and new substance applications.

Guidance materials are used to assess applications for EMA herbal medicine monographs and herbal medicine product. The monographs contain the Committee of Herbal Medicine Products (HMPC) opinion on actions, indications, safety information and interactions. In the European system traditional use constitutes at least 30 years of use preceding the date of application (with at least 15 years of that time has to be demonstrated use within the EU).

The Australian *Guidelines on the Evidence Required to Support Indications for Listed Complementary Medicines* (Evidence guidelines), state that applicants wishing to make traditional claims must be able to demonstrate 3 generations or 75 years of use. This duration is more than twice that required in the EU.

The TGA has been moving increasingly toward harmonisation with the EU, whose reference standards, guidance and reports are already well regarded and adopted in the form of existing EMA guidelines, the European Pharmacopoeia and assessment reports comparable overseas regulators. EMA monographs may be used as substantiating evidence for listed medicines. The Australian requirement of 75 years is vastly out of step, as is a proposal that EMA guidance is not applicable based on this disparity.

Recommendation 46 of the Review of Medicines and Medical Devices Regulation (MMDR) recommends that the TGA develop or adopt from comparable overseas regulators efficacy monographs for commonly used ingredients in listed medicines. Harmonising with the EMA criteria for traditional use would ease such a transition in the future, should the TGA choose adoption of herbal EMA monographs.

Further still, if the TGA were to accept 30 years as evidence of tradition of use, and move toward a monograph system similar to that of the EMA, the sharing and application of information and resources could occur in both directions between regulators, thus fulfilling on the objective of the International Engagement Strategy.

Deregulation, commerce and trade

The Deregulation Taskforce was established in 2019 primarily to implement the deregulation agenda in the business arena by identifying and removing unnecessary barriers to growth, investment and job creation.

The Deregulation Taskforce have been charged with focusing on the regulatory burden for food manufacturers. Whilst complementary medicines are regulated as a medicine in Australia, many companies export to countries where the same product is regarded as food, or are competing with global food and nutrition businesses who sell comparable products as foods (dietary supplements) – for both Australian and international consumers.

In order to export to many countries, products must already be listable in Australia. That is, contain listable ingredients, which could be substances that rely upon a tradition of use. If a substance needs to demonstrate a far longer period of use before it can even be included in a medicine, this radically reduces innovative capacity and commercial competitiveness for Australia in an international marketplace.

If Australian applicants are required to apply 75 years of traditional use before a new substance application can be made relative to Europe where this is 30 years, it introduces an immediate delay (of 45 years) for Australian product to enter the market place. This type of disparity stifles competition in a highly competitive international marketplace, impacting commerce, trade and investment, without any particular purpose other an arbitrary agreement made during the 1980's or 90's in the absence of other criteria.

Harmonising with the EMA criteria for traditional use is congruent with the TGA's own international engagement strategy, the Australian Government's economic and commercial objectives to reduce unnecessary regulatory burden.

Origin and Relevance of the 3 generation or 75-year principle

The consultation raises the question of both the origin and relevance of the 3 generation/75 year rule, if it is to be used as exclusionary criteria for the assessment of both new substance applications and evidence for complementary medicine products.

Members of Complementary Medicines Australia with decades-old service to the industry and engagement on Government policy (both before, during and after the inception of the Therapeutic Goods Act) recall that this was an in-principle agreement between the TGA and the industry in the absence of any other guidance or relevant principles at that time.

Importantly, it was designed as a general guiding principle, not as a hard and fast rule to be applied in all contexts. In other words, if there was suitable information to suggest that the 75-years was not necessary, that could be taken into consideration during an assessment. This would include the fact that international regulators may use different principles but are nonetheless suitable and reliable sources of information for the purposes of assessing complementary medicines.

Further, at that time, international alignment with similar regulations, and global trade and commerce matters, were not key factors, if considered at all. The global commerce environment at the time was also of far less relevance, with low amounts of exports occurring at the time and low importation of international competitor products by Australian consumers from e-commerce websites (which barely existed at that time). These matters did not figure prominently then as they do today. It is critical to apply the lens of the origin of the guiding principle against the modern-day context of regulation and trade.

In this context, a search of the relevance of this principle does not lead to any material that could be considered to be of such supportive significance of this principle to mandate the adoption of this principle as a rule upon which data from highly respected international regulators could be refused as irrelevant to the criteria for complementary medicine assessments of all types.

Safety and quality

The EMA has a highly commendable record as an expert medicine regulator and accordingly is recognised as one of seven comparable overseas regulators (COBs) which have met the rigorous criteria set by the TGA. The TGA accepts evaluation reports for prescription and other registered medicines from the EMA.

The EMA monographs are designed for the monograph based regulatory model of the European Union. Within this framework, the distinction between well-established use (15years) and traditional use (30 years) is part of the initial process to determine whether an ingredient is eligible to be classified in either of these ways. That is, if a substance does not satisfy the 30-year criteria it cannot progress through the evaluation process any further. If a substance does meet the criteria, it is then subject to rigorous safety and toxicity evaluation regarding its intended use. In either scenario, public interest is protected through process.

If the new substance meets the criteria for evaluation as a complementary medicine substance evaluation in Australia referred to on page 6 of this submission based on an agreement that the 30-year rule established by EMA is acceptable and relevant, Australian substances may then proceed to evaluation, however, safety and quality evaluation is still required. Thus, non-adoption of the annotation does not create any public health or safety concern.

Therefore CMA finds that adoption of the EMA guidance used to form EMA herbal monographs, would only strengthen the current regulatory framework and decrease unnecessary regulatory barriers for Australian businesses in respect of global competition and innovation.

Evidence

As mentioned previously, the expected flow-on impact of adopting this annotation, and further adoption through the TGA Evidence Guidelines for listed and/or listed (assessed) medicines, is expected to be extremely onerous and create significant regulatory barriers for the Australian industry, both within in Australia, as well as internationally.

Recently, the TGA have focused on the nature of various herbal preparation types. In Europe, Western Herbal Medicine is used extensively in a number of countries, such as Germany and Switzerland. Herbal extracts are continually undergoing methodology refinement, but have so more than ever during the 20th century, and are also increasingly likely to use other herbs that have been adopted from other non-European countries. It is not unreasonable to expect that Western Medical Herbalists within this context may well find that 30 years of use is sufficient to establish its therapeutic relevance and benefit, recognised by EMA as the regulatory body. In the absence of any information that there is an issue in Europe with that approach, and in the absence of any information to suggest that 75 years is necessary or has a critically meaningful underpinning, it is appropriate to continue with all aspects of international alignment with EMA and other comparable National Regulatory Authorities.

Conclusion

CMA thanks the TGA for the opportunity to be involved in the consultation on the adoption of the EU Guidelines. CMA supports the safety in use of medicines, specifically complementary medicines. Primarily we highlight the unnecessary mismatch between international regulatory guidance regarding definitions of traditional use and evidence categories and the critical necessity to align with international regulators on such matters, especially for complementary medicines which are low risk products within an internationally fluid trade environment.

In keeping with the trend toward cooperation and harmonization across regulatory jurisdictions; the Government agenda of reducing unnecessary regulatory barriers upon Australian businesses without compromising health and safety considerations; and the critical necessity of having equality of trade in an increasingly global commerce (including e-commerce) marketplace, CMA submits that:

1. The annotations in respect of EMA/HMPC/104613/2005 Rev. 1 and EMEA/HMPC/166326/2005 should not be adopted.
2. The Australian guidance regarding 75 years of tradition of use (both duration and evidence types) requires review with the view of discarding this rule such that Austalia is harmonised and aligned with that of comparable international authorities EU, Canada and others where relevant, particularly in relation to evidence reviews.