Complementary Medicines Australia *submission to the TGA consultation: Removing redundant processes for entering certain formulation information into a therapeutic goods application*

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CMA Response to the TGA consultation: Removing redundant processes for entering certain formulation information into a therapeutic goods application

Complementary Medicines Australia (CMA) appreciates the opportunity to provide feedback on the TGA consultation: Removing redundant processes for entering certain formulation information into a therapeutic goods application.

CMA is the peak body representing a thriving medicines sector supporting Australian jobs, research, manufacturing and exports by meeting community demand for preventative and complementary healthcare. The sector in Australia is a highly capable manufacturing industry required to comply with PIC/S GMP requirements including regular inspections, and strict mandatory pharmacopoeial and other TGA quality standards.

Australia's reputation for quality has evolved over several decades into an industry that is:

- A greater than $5 billion industry
- Exporting more than $1 billion annually
- Employing more than 29,000 Australians, primarily in skilled technical professions
- Since 2018, the largest category exporter to China, above formidable international rivals.

Australia maintains the highest quality manufacturing standards in the world for finished product complementary medicines including vitamins, minerals, and plant-derived preparations including standardised herbal extracts.

CMA is committed to a vital and sustainable complementary medicines sector and we support the safe use of substances and medicines, with access through appropriate and balanced risk-based regulation, while contributing to skilled local employment, health enhancement and preventative health strategies to help Australians live healthier lives and in turn, to reduce the burden on the healthcare system wherever possible.

Through this consultation, the Therapeutic Goods Administration (TGA) is seeking feedback on a proposal to streamline how information about certain therapeutic goods formulations is entered into TGA electronic systems when seeking market approval.

Specifically, the TGA propose to discontinue entering certain types of formulations into a subordinate database of ingredient mixtures (known as the Proprietary Ingredients Table) before they are selected into therapeutic goods applications for inclusion in the Australian Register of Therapeutic Goods (ARTG). The consultation states that under this proposal there would be no change to how a medicine is reviewed, or to the ingredient information that is displayed on labels or in the public summaries of medicines on the ARTG.

Proposal 2: Discontinue processing of non-specific Excipient Mixes into the Proprietary Ingredients Table

Proposal 2 intends to discontinue the use of non-specific Excipient Mixes which currently exist to capture a combination of purposes.

The consultation provides that this category can result in the mixture not validating in specific medicine application systems. Certain TGA medicine application systems rely on validation rules with limits on ingredients when used in a mixture with a specific purpose (i.e., flavours, fragrances and printing inks).

The consultation proposes to include any such mixes within the existing remaining Proprietary Ingredients Table categories, with a specific purpose assigned to them.

CMA recognises the need to amend the ingredients this category and ensure that validation systems are working effectively. Similar administrative changes in the past have often led to further inadvertent difficulties for industry including potential inadvertent, or allegations of, non-compliance during post market reviews in relation to ingredient specifications and product changes. In addition, this change would require changes not only to PI's but to product specifications and other quality control documentation used for each medicine, which represents a high burden and can take significant time to implement, particularly if a number of products are affected by the change.

The difficulty that previous consultations have shown is that changes such as this are quick to make the change initially but are not thorough in following through to ensure that industry are adequately

supported through any such transition, particularly sponsors, from an administrative, listing application and compliance perspective where changes are required.

With this consultation being coordinated by PSAB, we are concerned that the regulatory branch whom are currently in the midst of a large number of other reforms, do not have the time to devote to ensuring such changes can be implemented smoothly and that if problems arise, even years down the track, that there is a system in place to help rationally deal with any issues and does not result in Section 30 letters or misunderstandings resulting in allegations of non-compliance issues.

If this category needs to be removed and changes implemented, it must be done with an abundance of caution and support for both suppliers and sponsors, as well as significant implementation time as this issue affects the documentation of the entire supply chain.

We would also request that if suppliers have requests to implement new and specific categories to accommodate specific ingredient types that these are considered and CMA are happy to work through any specifics related to this in targeted work post-consultation.

Proposal 1: Discontinue processing of active ingredient mixtures into the Proprietary Ingredients Table

As a point of context, it is acknowledged that sponsors have had difficulty with PIs and have sought an improvement in approach – however, this is not limited to the 2 active categories that the TGA are proposing to remove – it affects all 14 of the categories and must be dealt with as a whole.

The stated purpose of the consultation is to:

- improve the integrity of the data held within the TGA's Ingredients Repository

CMA recognise that this needs to be critically done for all remaining 14 categories, not only the 2 active ingredient categories proposed for removal. Data integrity of the remaining 12 excipient categories is an equally important issue, which suggests that this consultation is not primarily about removing redundant processes or improving data integrity of PIs but is rather paving the way for a long-term change of policy and enforcement on whether such active PI mixes are required to have evidence of GMP licensing or clearance.

GMP considerations

Under Proposal 1, the TGA state that the use of PI numbers for mixtures containing an active ingredient is particularly confusing for suppliers and sponsors in relation to manufacturing and GMP requirements, and that there is considerable confusion whether the manufacture of such mixtures constitutes the manufacture of an intermediate therapeutic good, which would require the relevant manufacturing site to have TGA approval. Further, the consultation states that it is also thought to create confusion regarding the responsibilities of finished good manufacturers in relation to accepting such ingredient mixtures as raw materials when they may not have access to all relevant quality control data and that subsequently, the TGA propose to cease the processing of new Active Premix and Active Herbal Extract entries into the Proprietary Ingredients Table. As a result, this would limit the Proprietary Ingredient notification process to mixtures that only contain excipient ingredients.

The above confusion in relation to GMP is not necessarily related specifically to Proprietary Ingredients, there have been ongoing issues in relation to potentially changing expectations around evidence of GMP. The TGA and industry have had a specific policy about when and where TGA GMP clearance applies to listed medicines, which begins either at the manufacture of the dosage form or

generally the blending together of two or more ingredients. Under existing TGA policy and enforcement, there are not any processed materials (such as active PIs) that would be subject to a requirement to provide evidence of GMP (TGA Licensing or Clearance) for either overseas or Australian manufacturers (notwithstanding that there are cases where sponsors may have done so, and notwithstanding that as a matter separate from Listed medicine requirements under section 26A of the Act there have been some instances Australian facilities have been asked to hold a TGA license due to their jurisdictional locality in Australia unless they are specifically exempt). The evidence of this longstanding policy and enforcement was clearest in the 2011 version of the ARGCM and was more recently confirmed, and industry request for information about any change to this policy has not been met with further conversation other than the above statements in the consultation which tend to increase the concern over potential changes occurring without necessary discussions.

While some officers have held views about whether other intermediate active ingredient blends should require evidence of GMP (GMP clearance for example), this policy has not ever been communicated nor implemented for listed medicines. Evidence of GMP for such blends has only applied to registered medicines. This has also been reflected in the PI system not gathering evidence of GMP at the time an AP/AHP was listed, and some GMP officers have acknowledged that the presence of the PI system is viewed as a barrier to implementing different views on how GMP should be implemented. When the ARGCM (Australian Regulatory Guidelines for Complementary Medicines) was amended to start using words such as “may require” without any further information or clarification, industry sought clarification and a response was received after a considerable length of time affirming the long-standing policy and positions. Advice to the contrary has not ever been provided other than the vague and now additionally concerning statements regarding civil and criminal actions that are suggested in the current ARGLRCM (Australian Regulatory Guidelines for Listed Medicines and Registered Complementary Medicines). This collectively represents very concerning statement and developments from the TGA of a major shift in policy potentially without consultation, considering that the TGA has traditionally held a strong understanding of the global supply of ingredients used in complementary medicines, the risk level, and the cost and infrastructure challenges involved for products often with multiple low risk ingredients. As per our communication in December, any intended changes to prior and existing advice needs to be to be transparently discussed. Industry have requested the Complementary Medicines Technical Working Group begin

discussions around this issue considering the concern around potentially changing policies occurring without warning that has been generated by the proposed removal of these active proprietary ingredient formulations.

In particular, this is the case as any steps towards changing (increasing) policy and enforcement that would be seen as increasing regulation – and this would be seen as a very large increase in regulation as well as creating unforeseen damage to industry– which would be moving in the opposite direction to the wider Australian Government who are seeking to futureproof existing Australian manufacturing industries by providing lower regulatory burdens among other incentives, as part of the Modern Manufacturing Strategy (MMS) announced by the Hon. Prime Minister Scott Morrison MP.

Administrative considerations on removal of active proprietary mixes

For existing Active Premix and Active Herbal Extract entries, the TGA have proposed:

- to inactivate any PI numbers in these categories not linked to current ARTG entries
- where an affected PI is used in an active ARTG entry (to be considered case-by-case):
    - to allow continued use with no further action or
    - to allow sponsors to update their medicine formulations to replace the PI number with the individual constituent ingredients within their ARTG entries. The TGA may consider whether a transition period would be needed for the sponsor to update their ARTG entries.
- reduce unnecessary work for active ingredient suppliers, such as the need to submit details of their mixture to the TGA

The main active ingredient suppliers express a preference for maintenance of the system. The ability to update/maintain details for all 14 categories is required to ensure sponsors are able to use PIs with greater confidence. While we understand most suppliers prefer to use the system, for those that do not, greater clarity that they do not need to, is also welcome.

- remove redundant processes that are resource intensive for TGA and industry

Some sponsors express a preference for the removal of PIs, but this relates to most excipient categories (except F/F/C/PI) not only the 2 active ingredient categories, and the only reason for this preference is the issues with data integrity which will continue to exist for the other 12 categories

and thus does not address the core industry issue. For all 14 categories, suppliers have expressed difficulties in maintaining the database, and sponsors in maintaining accurate records due to data integrity. If this were fixed through improvements in the TGA digital transformation project, it would not be necessary to remove these 2 active categories.

Whilst some sponsors prefer not to use, or to avoid PIs from many categories, active and excipient, this has been due to the dysfunctionality of the system. This might include active PIs, but also other PIs, such as capsule shells, coatings, preservative mixes, etc. There are also some sponsors who prefer to use a variety of active and excipient PIs for ease of use as they find they are a lower administrative burden.

Therefore, it cannot automatically be assumed that the removal of active (or other) PIs will result in perceived lower administrative burdens for sponsors generally. Naturally, some sponsors fall between these two ends and limit the use of some PIs but actively engage with the use of some PIs, both active PIs and a range of excipient PIs.

The remaining issues of legislative basis, administrative burden and data integrity/lifecycle management, are no different between the three proposed categories to be removed and the remaining 12 categories. This includes 'flavours, fragrances, colours, and printing inks' which are sometimes dealt with separately due to their long and complex list of ingredients – for example, the term 'colour' 'flavour' or 'fragrance' is printed on the public ARTG entry rather than the full list. The other 8 excipient categories are also of concern and not of any substantive difference to the 2 active PI categories, nor is the view that the 2 active PI categories might only have a short ingredient list for sponsors to enter on the ARTG substantially relevant due to the various matters outlined in this response.

Sponsor perspective and concerns.

Sponsors have a range of reactions and approaches to PIs. There are some sponsors who prefer not to use or to avoid PIs from many categories, active and excipient. This might include active PIs, but also other PIs, such as capsule shells, coatings, preservative mixes, etc. Sponsor concerns arising relate primarily to inefficiencies in suppliers updating the system and the ability of ARTG records to reflect those changes adequately. The ARTG concerns are not eliminated by the removal of PIs as the changes

to the ARTG system required for sponsors to be able to update their records without excess fees has been under discussion but has not yet been implemented by the regulatory branch (COMB).

There are also some sponsors who prefer to use a variety of active and excipient PIs for ease of use as they find they are a lower administrative burden. Therefore, it cannot automatically be assumed that the removal of active (or other) PIs will result in perceived lower administrative burdens for sponsors generally.

Naturally, some sponsors fall between these two ends, and limit the use of some PIs but actively engage with the use of some PIs, both active PIs and a range of excipient PIs.

Data integrity – at the time of Listing

Feedback from our members is that the top main concern – whether for excipient or active PIs – is that sponsors do not have full certainty that the necessary data is enmeshed with the TGA's record of the PI, especially restricted excipients, unless it can be cross-referenced on the TGA system before the medicine is listed onto the ARTG. This has always been a concern for sponsors but has become heightened in recent times. If sponsors were able to vet the excipient names at the draft listing stage, this would help them verify the data that they hold is consistent with the TGA's record for all 15 categories. Having a second verification in this way does not indicate any failure of any primary system, it simply underscores the fact that having a second system of verification is part of a positive and streamlined system of controls and checks to further ensure accuracy and safety, a goal supported by Government. To emphasise, there is no difference between active and excipient PIs in this respect, and thus no value in separating out active PIs.

Recognising this approach may not be possible for flavours, fragrances, and colours, these excipient mixes should instead at least be flagged for sponsors in the ARTG system when they have at least one restricted ingredient or component, such as caffeine.

Without this ability, sponsors must certify based on the information that they have available, and if that information turns out to be incorrect at no fault of the sponsor, then sponsors have spent a significant listing application fee of $860 on a product that they may not wish to sponsor in order to meet ability to satisfy customers, to meet safety and labelling expectations, and to ensure eligibility for listing and make proper certifications under section 26A of the Act.

This is where potentially administrative and cost burden, and liability risk enters for sponsors. Importantly this key concern is one that applies to all categories, especially the proposed remaining list of excipient categories, and must be managed for all categories in the short and long term, it is not relevant to separate out active PIs only.

Data integrity/management – during the lifecycle of the product

Similarly, there is not a good system in place for lifecycle management of all active and excipient categories of PIs, which negatively affects sponsors as well as suppliers as well as the key point of having potential flow on effects to consumers. This has also been a key issue.

The removal of 3 PIs only has no benefit on the above, as the problems remain in place:

- For existing listings with existing PIs, the inability to manage the data over the lifecycle of both the PIs and the products with PIs remains present and remains a difficult and costly issue for suppliers and sponsors to manage.
- If the 2 active PIs are removed, the same lifecycle management issues exist for sponsors. If there are any changes in excipients, there is a very expensive, high burden flow-on effect for sponsors by managing ARTG entry changes and costs. A cost-effective solution must be devised, whether excipient changes occur as part of PI change or a product change that is not PI related. In this respect, a number of issues were identified through ComTech in relation to the complexities but most importantly the unnecessary costs of updating formulations on the ARTG. It is inconceivable that changes to any system could move forward without those changes being finalised in a positive, cost-reduction manner for industry under MMS.

Data currently not available to sponsors in Active Herbal Proprietary Ingredients

The consultation document provides that "Including an ingredient mixture in the Proprietary Ingredients Table does **not** provide any data exclusivity or intellectual property protections".

Whilst this statement is made and may be true from a strictly IP perspective, it does not acknowledge that the system does provide some functional protection. This functional protection is still afforded to suppliers of colours, flavours, fragrances, and printing inks. This asks the question of why some ingredients are afforded a functional protection and others are not.

Some suppliers hold the view that if a researched extract cannot have some elements functionally protected from potentially generic copies of the extract occurring, that it may not be worthwhile to continue to supply an ingredient, or to supply a new ingredient to Australia, considering that the proprietary protections in other countries are often higher, such as the USA where more details are permitted to be proprietary or functionally protected.

The key reasons are the ability to potentially copy the key aspects of an extract (herbal input, ratios, solvents, component levels etc) without capturing other also important aspects that may relate to that extract and without the owner of the research obtaining any return to recoup the costs of conducting research. This is more relevant if there is proprietary research attached to the extract. Some note that it could be a disincentive to conduct research if the researched extracts were copied. This is a risk to some suppliers more than others, as some do not object to sharing full information however, the risk for those suppliers needs to be noted and should be acknowledged that it isn't practically different to the functional protection provided to F/F/P-Inks/Colours, particularly as the latter category conduct far less research in order to obtain market access than AP/AHE ingredients.

Some major suppliers therefore feel that the removal of active PIs would have an impact on their operations and the influence on wider industry, just as removing excipient PI categories for excipient PI suppliers would be expected to have an impact.

Whether it is the 2 active PI categories, or the other 12-13 excipient PI categories, suppliers do not support partial removal of some categories in the near term, but support a longer term view whereby all categories are re-assessed simultaneously as part of a consultation that has the view of:

- Implementing improved data management systems, especially throughout the lifecycle, in a way that positively benefits suppliers, sponsors, and consumers. This would occur best during the TGA Digital Transformation project and after the positive ARTG management changes referred to above.
- As part of this longer term view, suppliers are willing to be consulted on alternative mechanisms to the current management, for example, cost recovery as an option. PI suppliers have noted that it would not be fair if some PI categories were removed altogether whilst other categories continue unaffected under cost recovery arrangements but without all of the same issues that affect all 15 categories for sponsors being addressed. Like sponsors, suppliers agree that removing active PIs in a piecemeal fashion from the remaining 12 excipient PIs does

not offer any meaningful improvement to any of the core issues faced for PI management in totality.

Effective management for existing Active Premix and Active Herbal Extract entries in the Proprietary Ingredients Table

Some suppliers and sponsors choose not to use the PI system for all 14 categories. Others prefer to use PIs including AP/AHEs from the perspective of reduced burden and easier administration, whilst acknowledging that this system needs to be more functional for all 14 categories.

Provided that both suppliers and sponsors are under no obligation or implied obligation to use either AP/AHE ingredients or other excipient PIs, those who prefer to use them should not be prevented from doing so.

Better, more flexible data integrity and lifecycle management options for all proprietary ingredients need to be implemented as part of the Digital Transformation project. A significant improvement to the management of them may attract the increased use of them as a more streamlined system with a central validation point that can be easily referenced on product specifications, which also helps to clearly establish the supply chain link for the purpose of post market reviews and to reduce regulatory burden for sponsors.

While retaining a system would not reduce TGA burden, it has a very high potential to meet preferred goals of the TGA, including having oversight and notification of ingredient changes within products, and an efficient method of ensuring sponsors are aware of changes, and make new certifications against updates. All of this helps to ensure:

- best practice safety and quality management of products including changes that might affect safety and ensuring that sponsors are properly notified of them, especially listed products
- ongoing incentivisation of research into traditional, herbal, and other complementary medicines, by ensuring that suppliers continue to have access to a system that helps them have confidence in the ability to functionally restrict the blatant copying of their extract, potentially in a different or even substandard manner.
- support of the larger Government goals under the Modern Manufacturing Strategy to help ensure that manufacturing related businesses have the tools and systems available to them to encourage scaling up, in particular, that there is confidence in a system whereby herbal

extracts and other ingredient suppliers have a reliable way of maintaining a central reliable reference source.

The retention of existing AP / AHE ingredients could, through the new Digital Transformation system, be envisaged as follows, as a suggestion for further workshopping:

- Suppliers have no objection to paying a nominal fee to optionally include new AP/AHE's in the database, and to make changes to content of existing products.
- Changes would need to be compatible with those which do not trigger a "New" product as per the document, Changing a listed or assessed listed medicine: application levels and change tables, also accounting for the allowances in the Guidance on equivalence of herbal extracts in complementary medicines. For example, solvent ratio, amount of herb to make a standardised extract, excipients, component ratio.
- Sponsors should not be liable for any fees, noting that sponsors will incur costs in other ways, including changing product manufacturing documentation in the minimum.

Whilst we are sympathetic to the challenges of the PI system and to various concerns by various stakeholders, this is all the more reason to make sure the right approach is taken in the shorter term and longer term for all active and excipient PIs, and that the core issues affect all categories, not only the active categories. Therefore, we do not agree that this is the correct approach to reducing administrative burden or costs without a wider review, in fact, it may exacerbate them. Rather, we propose other measures may be more effective.

Long term, all-inclusive review of Proprietary Ingredients

1. CMA supports a longer-term review of the entire proprietary ingredient system including all categories for the core issues which relate to data integrity and lifecycle management, if it is done as one complete review at one time. This will serve the larger Government's view of ensuring there are deregulatory measures in place to support the goals of the Modern Manufacturing Strategy. Thus, the project should wait until it can be properly incorporated with other positive TGA reforms that help industry, namely both of the following:

   a. Incorporation into the TGA Digital Transformation project, a project which has been supported by CMA, to allow proper data integrity and lifecycle management of all 14 categories at lowest possible burden to all stakeholders. With the advancements in supply

chain management, this could conceivably include alternative systems whereby a code held by suppliers can be used simultaneously by TGA electronic systems as well as sponsor electronic systems.

b. Review after mechanisms have been meaningfully implemented to support low or no-cost changes to ARTG records by sponsors that was introduced by the ATGC and supported by CMA and CHPA. This has been under examination during 2019 and 2020 in ComTech. Standing action items need implementing to support the goals of the MMS, and before advancing any administrative changes to PIs. These changes include investigating statutory timeframes for section 9D(1) changes; investigating the possibility of making multiple grouping changes for Listed medicines during one application without creating a new AUST L number, which is consistent with other TGA areas; and investigating flow-on implications from a cost-recovery perspective if all/some ARTG changes were free.

Short term goals:

1. The main concern for sponsors who are currently using PIs is around data integrity/lifecycle management and associated costs, which will exist with or without PIs on the TGA database. This would be dealt with in the shorter term, in as much as possible, by ensuring that the excipients (but not quantities or proportion of excipients) of all categories of PIs (other than flavours, fragrances, and colours) are visible in the draft ARTG listing, as well as the sponsor's ARTG listing, both of which are equivalent to their existing viewing on the public ARTG record which occurred under the recent public consultation. This is with the exception of flavours, fragrances and colours that could have a flag if they contain restricted ingredients or components. Until better systems could be put into place as part of the Digital Transformation project, such an approach could help sponsors as a useful secondary system to help industry and consumers, which eases the burden on a number of a levels for sponsors, and also eases unnecessary regulatory burden for manufacturers at the manufacturing step 'release for supply'.

2. A further positive short term measure is that, if there are any known issues for existing proprietary ingredients, such as the incorrect equivalent quantity of vitamin preparations or other minor data issues, we encourage these to be rectified on a case-by-case basis, whilst

ARTG entries are updated free of charge, followed by a 2 year transition to rectify labels or other information.

3. The concern around unnecessary listing of PIs and/or some delay to sponsors and/or misconception around the purpose of PIs relating to claims, present much more minor concerns and ones that can be easily and effectively be dealt with by improved guidance from the TGA, as well as communication by CMA and others to ensure any misconceptions are resolved.

Effective management of ARTG entries that use the affected PI numbers in their formulations

Changes must not be required for existing products, including existing products that undergo grouping applications, unless the sponsor chooses to make the change at the time. As per the above, an integrated and future-proof system of managing PIs effectively is preferable to removing them in the short term and re-implementing a new system that will inevitably occur at a later date.