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| Removing redundant processes for entering certain formulation information into a therapeutic goods application |
| Public consultation |
| Version 1.0, January 2021 |

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## Overview

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, we 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](https://www.tga.gov.au/artg)[[1]](#footnote-1) (ARTG).

Under this proposal there would be no change to how a medicine is evaluated, or to the ingredient information that is displayed on labels or in the public summaries of medicines on the ARTG.

### Scope

The focus on this activity is limited to ingredient mixtures that contain an active ingredient (known as ‘Active Premixes’ and ‘Active Herbal Extracts’), and non-specific ‘Excipient Mixes’, which do not provide sufficient information on the purpose of the mixture.

Through this activity we seek to:

* improve the integrity of the data held within the TGA’s Ingredients Repository
* reduce unnecessary work for active ingredient suppliers, such as the need to submit details of their mixture to the TGA, and
* remove redundant processes that are resource intensive for TGA and industry.

The scope of this consultation paper is purposely limited to the above categories. We recognise that there have been calls for a broader review of the overall policies or processes for all categories of mixtures in the Proprietary Ingredient Table. However, the benefits and challenges associated with entering mixtures into the Proprietary Ingredients Table are different depending on the mixture’s purpose and formulation.

## Why we are consulting

We are seeking your views on:

* how our proposal to stop processing new Active Premixes, Active Herbal Extracts and non-specific Excipient Mixes into the Proprietary Ingredients Table would affect you
* the proposed approach for managing these types of entries previously entered into the Proprietary Ingredients Table.

We invite you to provide your feedback by completing our online survey (click on the link below).

We will consider any feedback received before a decision is made. We will also publicly announce the outcomes of this consultation and publish your responses, unless you specifically request that they be kept confidential.

Once decided, we aim to implement the proposal in the first half of 2021. The TGA’s Proprietary Ingredient processes are purely administrative. No legislative changes would be needed to implement this proposal.

**Have your say**

Invitation to provide feedback – online survey

## Background

### Formulations of therapeutic goods in ARTG entries

The Australian Register of Therapeutic Goods (ARTG) is a database within the TGA’s electronic-Business System (TBS). Each therapeutic good (medicine, device and biological) approved for sale or supply in Australia must be entered on the ARTG, unless exempt.

Each electronic ARTG record contains information about the ingredients within that good’s formulation. This includes information on the role that each ingredient plays in the formulation (i.e. as a therapeutically active ingredient or as an excipient):

* medicines and biologicals can have both active ingredients and excipients
* other therapeutic goods (such as disinfectants) can only contain ingredients marked as excipients within the electronic system.

### Ingredients Repository

The TGA maintains a database of ingredients used to describe the formulations of therapeutic goods on the ARTG, termed the Ingredients Repository. This Repository is composed of two tables:

* Ingredients Table - contains the names that have been approved for ingredients used in the formulations of therapeutic goods on the ARTG.
* Proprietary Ingredients Table - contains information about mixtures of ingredients, known as ‘proprietary ingredients’ or PIs. The formulations of entries in the Proprietary Ingredients Table use ingredient names sourced from the Ingredients Table.

Entries in the Ingredients and Proprietary Ingredients Tables can be viewed on the [TBS website](https://www.ebs.tga.gov.au/), under Public TGA Information.

#### Types of formulations in the Proprietary Ingredients Table

Ingredient mixes in the Proprietary Ingredients Table must have an identified role or purpose, with 14 categories available. Most categories are for mixes containing only excipient ingredients; two categories contain a therapeutically active ingredient, as outlined below:

* Active pre-mix - *contains an active ingredient*
* Active herbal extract - *contains an active ingredient*
* Adhesive
* Capsule shell formulation
* Coating material
* Colour
* Cream (Ointment) base
* Excipient mix *– non-specific categor*y
* Flavour
* Fragrance
* Ink
* Oral base
* Preservative mix
* Sweetener

#### Creating entries in the Proprietary Ingredients Table

Ingredient suppliers wishing to enter their mixture into the Proprietary Ingredients Table submit a form to the TGA with information about the constituent ingredients in their product, the mixture’s purpose and which types of therapeutic goods the product is intended to be used in. Once entered in the Table, a unique ‘PI’ identification number is auto-generated.

Additional administrative steps are required where an ingredient mixture is intended for use in a listed medicine. For each such mixture entered into the Proprietary Ingredients Table, validation rules need to be manually encoded to allow applications containing that mix to validate in the listed medicines system. These rules need to be created in addition to existing validation rules for individual ingredients.

The process for entering new mixtures in the Proprietary Ingredients Table and creation of validation rules typically takes up to 20-30 working days.

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| Information | **Points of clarification**   * Entering a formulation into the Proprietary Ingredients Table and allocation of a PI number is an administrative process with **no legislative basis**. * Issue of a PI number does **not** mean that the mixture is approved by the TGA for use in therapeutic goods - we do **not** check whether the formulation meets specific regulatory requirements for use in therapeutic goods when it is entered into the Proprietary Ingredients Table. * The ingredient mixture is **not** evaluated for safety, quality or efficacy before it is entered into the Proprietary Ingredients Table. * Including an ingredient mixture in the Proprietary Ingredients Table does **not** provide any data exclusivity or intellectual property protections. * You do **not** need a PI number to be able to sell your ingredient for use in the formulation of a therapeutic good or to claim that your mix of ingredients is unique or has a specific mode of action. * The manufacture of mixtures in the Proprietary Ingredients Table that contain an active ingredient may be considered a step in the manufacture of the finished product and a TGA Good Manufacturing Practice (GMP) licence or approval of the manufacturer may be required, unless exempt. |

### How data from the Ingredients Repository is used in ARTG entries

Applicants can select individual ingredients from the Ingredients Table or mixtures from the Proprietary Ingredients Tables to describe the formulation of their therapeutic good in their TBS application. Regardless of which Table is used, the sponsor of the therapeutic good retains legal responsibility for the information in their ARTG entry and that the product meets relevant safety, quality and efficacy standards.

Once a medicine or biological is approved, relevant ingredient data from the Ingredients Repository is visible in the good’s public ARTG summary. For example, each ARTG entry automatically displays the approved name and quantity of the active ingredient(s), regardless of whether the constituent ingredients were selected individually from the Ingredients Table or as a mixture from the Proprietary Ingredients Table.

For [most types](https://www.tga.gov.au/proprietary-ingredient-formulations-and-how-they-are-used)[[2]](#footnote-2) of excipient proprietary ingredient mixtures, the names of the constituent ingredients in a good’s (biological and medicine) formulation are also visible in the public ARTG summary.

#### Changes to ingredient mixtures

To maintain the integrity of data within the ARTG, we do not allow changes to be made to entries in the Proprietary Ingredients Table once they have been created. If an ingredient supplier changes the name or formulation of a mixture, the existing entry in the Table cannot be updated. Instead, the supplier can request to create a new Proprietary Ingredients Table entry with the updated formulation, which would trigger a new PI number. Sponsors of affected therapeutic goods that use that mixture in their goods are required to make consequential changes to their ARTG records.

#### Discontinued ingredient mixtures

If a mixture has been discontinued by its supplier, the relevant Proprietary Ingredients Table entry cannot be inactivated in the Table if there are any active ARTG entries linking to that PI number. This can be problematic as there are numerous ARTG entries active in the system where the therapeutic good is not being supplied.

It is also common for ingredient suppliers to not inform the TGA where a mixture is no longer being supplied, and for ingredient suppliers to be allocated a PI number for a formulation that is never used in goods on the ARTG. This may be because on evaluation the mixture may not have met relevant standards for a particular therapeutic good or the sponsor chose to enter the constituent ingredients individually into their ARTG application. Together, these issues impact on the currency of the data held within the Ingredients Repository.

### Opportunity to streamline administrative steps

The Australian Government recently [announced](https://www.health.gov.au/ministers/the-hon-greg-hunt-mp/media/digital-transformation-to-deliver-more-timely-medicines-for-australians-and-improve-patient-safety)[[3]](#footnote-3) a digital transformation of TGA’s electronic systems to improve therapeutic goods regulation processes. To ensure that future TGA electronic systems are efficient and fit for purpose, it is timely that existing administrative processes are clarified and streamlined where possible.

Administrative processes associated with three categories of Proprietary Ingredients mixtures were identified as redundant and resource intensive or did not fit within the broader purpose of the TGA’s proprietary ingredient system. The following changes are proposed:

1. Discontinue processing of active ingredient mixtures (Active Premixes and Active Herbal Extracts) into the Proprietary Ingredients Table.
2. Discontinue processing of non-specific Excipient Mixes into the Proprietary Ingredients Table.

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

### About active ingredient mixtures

The Proprietary Ingredients Table displays 793 entries that contain a therapeutically active ingredient:

* 523 entries are categorised as an Active Premix. These mixtures typically consist of one active ingredient and between 1-3 common excipients. Common active ingredients in these mixtures are vitamin ingredients, such as cyanocobalamin or colecalciferol, and paracetamol premixes.
* 270 entries are categorised as an Active Herbal Extract. These herbal mixtures typically consist of one active ingredient, or an active ingredient and one or two common excipients, such as maltodextrin or silicon dioxide.

For these categories, the main ‘proprietary’ information relates to the manufacturing process, which is either not required to be entered in the ARTG (and not held in the Proprietary Ingredients Table), or to which the sponsor of the therapeutic goods is already required to have access[[4]](#footnote-4).

Use of PI numbers for mixtures containing an active ingredient is particularly confusing for suppliers and sponsors in relation to manufacturing and GMP requirements. 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. It also creates 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.

### Streamlining administrative steps

We propose to cease the processing of new Active Premix and Active Herbal Extract entries into the Proprietary Ingredients Table. The main driver for this activity is to limit the Proprietary Ingredient notification process to mixtures that only contain excipient ingredients. No changes to existing legislation or IT systems would be required to implement this proposal.

For existing Active Premix and Active Herbal Extract entries, we propose:

* 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.

#### How does this affect suppliers and sponsors?

Ingredient suppliers:

* will continue to be able to sell these types of formulations to prospective sponsors for use in therapeutic goods.
* will not need to submit a notification form to the TGA to enter the formulation into the Proprietary Ingredients Table. Instead, they will need to provide the relevant details of the constituent ingredients to the prospective sponsor for them to enter into their ARTG application.
* in some circumstances, will no longer need to contact TGA to establish or maintain a TBS client ID or maintain the details associated with their ingredient mixture within TGA electronic databases (including where supply arrangements for the mixture have been on-sold to other ingredient suppliers or where a business has undergone a name change).

Sponsors:

* will not need to wait for a PI to be entered into the Proprietary Ingredients Table before submitting their therapeutic goods application.
* will need to obtain relevant formulation details and enter these into their ARTG application instead of selecting a PI mixture. For listed medicines applications, quantities of some excipients are not required to be entered into the electronic system for the medicine to meet listing requirements.

#### What is not changing?

There is no change to:

* the amount or type of information made public about ingredients in a therapeutic good in the medicine’s or biological’s public ARTG summary, i.e. the names, amounts and equivalent information (where relevant) for active ingredients and the names of excipient ingredients.
* the need for correspondence between suppliers and sponsors about whether an ingredient mixture meets relevant requirements for use in a therapeutic good.
* the need for correspondence between suppliers and affected sponsors where there has been changes to a mixture’s formulation or other details.
* GMP requirements for the manufacture of therapeutic goods.
* the ability for sponsors to make claims about the formulations of their therapeutic good.

### Questions

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|  | * Do you support the above proposal? Why/why not? * Do you have any other suggestions for:   + managing existing Active Premix and Active Herbal Extract entries in the Proprietary Ingredients Table?   + managing ARTG entries that use the affected PI numbers in their formulations? * [Sponsors] Are there any educational or guidance materials you may need to assist you in entering your product’s formulation details into TGA systems? |

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

### About non-specific Excipient Mixes

The Proprietary Ingredient Table displays 580 entries within the non-specific ‘Excipient Mix’ category, with high variability in the types of ingredients contained within these mixtures. Unlike other categories in the Table, this category does not provide sufficient information on the purpose of the mixture.

Whereas some of the mixtures have trade names that include wording that indicates the purpose (e.g. moisturising base) other mixtures appear to be combinations of purposes (e.g. a capsule shell mixture that includes a flavour mixture). Some historical Excipient Mix entries consist of a sole ingredient (instead of a mixture) with information about that constituent ingredient available publicly through the supplier’s website.

### Streamlining administrative steps

We propose to cease the processing of new non-specific Excipient Mixes into the Proprietary Ingredients Table.

Use of non-specific Excipient Mixes to capture a combination of purposes 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). Where these types of ingredients are combined with others in a non-specific Excipient Mix, the electronic system is not able to accurately apply the validation rules to the medicine application.

It would be more appropriate to include any such mixes within the existing remaining Proprietary Ingredients Table categories, with a specific purpose assigned to them.

For existing Excipient Mix entries in the Proprietary Ingredients Table, we propose:

* 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):
  + reclassify existing mixtures into other categories. For example, numerous entries in this category include ‘moisturising base’ in the title, implying that the ‘Cream (ointment) base’ category would be more appropriate for the mixture. TGA could write to the affected suppliers requesting that they select a more appropriate category, noting that this may affect the mixture’s validation in certain TGA application systems.
  + allow sponsors to update the formulations of their ARTG entries from the PI number to instead select individual constituent ingredients. In this situation, TGA may consider whether a transition period would be needed for the sponsor to update their ARTG entries.

#### How does this affect suppliers and sponsors?

Ingredient suppliers wishing to enter a mixture of excipient ingredients into the Proprietary Ingredients Table would need to select one of the remaining excipient categories for their formulation. Where they supply a product that includes ingredients with more than one purpose (e.g. a flavoured capsule shell) they could either:

* submit multiple Proprietary Ingredient notification forms to create separate PI entries in the Table (e.g. one for the capsule shell component and one for the flavour component). The sponsor would then select each PI number into their therapeutic goods application; or
* provide details of the constituent ingredients of the mixture to the sponsor (e.g. either the capsule shell component, the flavour component or both) to allow them to individually enter these ingredients into their therapeutic goods application.

This activity is expected to clarify the purpose of ingredients used by therapeutic goods sponsors and remove any perceived need for active ingredient suppliers to notify TGA of their formulation before a sponsor wishes to submit their medicine application. This will also improve the quality of information within the ARTG and other TBS databases, providing greater confidence for sponsors and improved efficiency of TGA pre- and post-market activities.

### Questions

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|  | * Do you support the above proposal? Why/why not? * Do you have any other suggestions for:   + managing existing Excipient Mix entries in the Proprietary Ingredients Table?   + managing ARTG entries that use the affected PI numbers in their formulations? |

Version history

| Version | Description of change | Author | Effective date |
| --- | --- | --- | --- |
| V1.0 | Original publication | SOMS/SEB | January 2021 |

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1. <https://www.tga.gov.au/artg> [↑](#footnote-ref-1)
2. <https://www.tga.gov.au/proprietary-ingredient-formulations-and-how-they-are-used> [↑](#footnote-ref-2)
3. <https://www.health.gov.au/ministers/the-hon-greg-hunt-mp/media/digital-transformation-to-deliver-more-timely-medicines-for-australians-and-improve-patient-safety> [↑](#footnote-ref-3)
4. For [complementary medicines using herbal extracts](https://www.tga.gov.au/publication/guidance-equivalence-herbal-extracts-complementary-medicines), the type, concentration and quantity of extraction solvent, will affect the spectrum of components obtained from a given amount of herbal material. Currently, sponsors are required to nominate both type and concentration of solvent in their product applications, but not the quantity of solvent used. [↑](#footnote-ref-4)