Australian Government
Department of Health
Therapeutic Goods Administration

Consultation: Business process improvements supporting complementary medicines assessment pathways

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TGA Health Safety Regulation

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Purpose and scope

The Therapeutic Goods Administration (TGA) is seeking comments on a number of reforms that will deliver a more flexible, predictable, efficient and transparent regulatory framework for complementary medicines.

Specifically, we are seeking feedback on the following:

- The introduction of risk-based application categories for pre-market assessments.
- Proposed application requirements, business processes, legislated assessment timeframes and fee structure for applications in each category.
- A set of minimum data requirements to standardise complementary medicine pre-market assessments.
- Criteria and mechanisms for acceptance of reports from comparable overseas regulators and alternate sources of evidence for *de novo* assessments.
- Strategies to enhance the post-market monitoring and compliance scheme for listed medicines.

While we have previously consulted on the proposed use of evaluation reports from comparable overseas regulators for prescription medicines and medical devices, this consultation focuses on complementary medicines only.

Background

The Expert Panel conducting the Expert Review of Medicines and Medical Devices Regulation (MMDR review) made 19 recommendations to improve the regulatory framework for complementary medicines manufactured, supplied and/or exported from Australia.
On 15 September 2016, the Australian Government released its Response to the Review of Medicines and Medical Devices Regulation.

The Government has agreed to implement reforms to:

- Introduce a new assessment pathway for listed complementary medicines that sits between existing low risk listed medicine pathway and the higher risk registered medicine pathway (Recommendation 39).
- Allow use of reports from comparable overseas regulators for the assessment of new ingredients, new registered medicines and products assessed through the new listing pathway (Recommendation 36 and 40).
- Broaden the range of acceptable sources of evidence for the assessment of ingredients proposed for use in listed medicines (Recommendation 35).
- Introduce legislated timeframes for complementary medicine and ingredient assessments (Recommendation 41).
- Enhance the post-market compliance monitoring scheme for listed complementary medicines (Recommendation 49).

A number of business process improvements will also be necessary to implement these reforms, including a revised fee structure, standardised dossier format and minimum data requirements.

Implementation of these recommendations will streamline our assessment and registration processes, enhance predictability for industry and improve timely access by Australian consumers to new complementary medicines that are safe and of good quality.

We consulted on the introduction of a new pre-market assessment pathway for 'assessed listed medicines' earlier in 2017.[1]

This consultation builds on these proposals by outlining application types, sources of evidence, business processes and timeframes that should apply to these assessments.

Objectives of the reforms

The objectives of these reforms are to:

- Provide an appropriate benefit/risk model for the evaluation of complementary medicines.
- Reduce duplication of regulatory effort through use of evaluation reports from overseas regulators of equivalent standard.
- Improve the quality of complementary medicine applications.
- Improve flexibility for applicants about the types of information that can be used to support pre-market applications.
- Improve the efficiency of complementary medicines evaluations.
- Provide consumers with timely access to high quality, safe and effective complementary medicines.
- Deliver appropriate cost recovery of complementary medicines regulation.
- Provide greater transparency and predictability of the regulatory process for all stakeholders.

Risk-based approach to regulating complementary medicines: three assessment pathways

The Australian regulatory framework for complementary medicine products and ingredients is based on risk. The amount of regulatory oversight and compliance effort needed to appropriately manage risks depends on the nature and intended use of the product. For example, products that include active ingredients with a long history of safe use, such as calcium carbonate, are not required to be assessed to the same level as a new ingredient.

[1] TGA, Consultation: Reforms to the regulatory framework for complementary medicines: Assessment pathways (last updated 14 February 2017). Available at: <https://www.tga.gov.au/consultation/consultation-reforms-regulatory-framework-complementary-medicines-assessment-pathways>.

There are currently two risk-based pathways through which a sponsor can obtain an approval to market a complementary medicine:

- **Listed medicines** are considered to be low risk based on their ingredients,[2] indications, and the way they are presented and administered. As such they can be entered on the ARTG following self-assessment and certification by the sponsor of the safety, quality and efficacy of the product.
- **Registered medicines** are considered to be higher level risk based on their ingredients[3] and indications. A medicine may only be included in the ARTG after a full assessment of the safety, quality and efficacy of the product by us.

The current assessment pathways only allow for assessment of low and higher risk medicines. The introduction of the new pathway for **assessed listed medicines** will allow us to better align the level of assessment with the risk and effort associated with evaluating intermediate risk complementary medicine products.

There is still scope, however, to adopt a more risk-based approach within each assessment pathway to more appropriately align regulation with risk posed by the regulated product.

Risk-based application categories for pre-market assessment pathways

We are proposing to introduce risk-based application categories to provide greater flexibility in the pre-market evaluation of complementary medicines. These application categories will sit within each of the complementary medicines pre-market assessment processes: new ingredients proposed for use in listed medicines, the assessed listed medicines pathway and the registered medicines pathway. The categories will differ in the amount and type of information we will need to review, the degree of scrutiny necessary before the product or ingredient can be made available in Australia and the assessment timeframe.

Complementary medicines containing well-understood active ingredients and 'clones' of existing medicines will fall into the lower risk categories, while more complex applications such as those involving new active ingredients or new indications will fall into the higher risk categories. Applications submitted in the lower risk categories will require less supporting information and will have shorter assessment timeframes than applications in higher risk categories. Minimum data requirements will be established to assist sponsors to understand the level of information required to support an application under each of these categories.

The proposed application categories for new ingredients (**Table 1**), assessed listed medicines (**Table 2**) and registered complementary medicines (**Table 3**) are set out in the following pages. A proposed new fee structure to support the risk-based application categorisation is also proposed to reflect work effort associated with the different application categories.

[2] Listed medicines must only contain low risk ingredients in acceptable amounts as specified in the Therapeutic Goods (Permissible Ingredients) Determination. Ingredients must not be included (or meet the criteria for inclusion) in a schedule to the Poisons Standard.
[3] Registered complementary medicines can include ingredients included (or that meet the criteria for inclusion) in a schedule to the Poisons Standard, other than Schedule, 4, 8 or 9.

Application categories – approach and purpose

We are proposing to undertake pre-market assessments in two ways – one for the use of reports from comparable overseas regulators, and a second for *de novo* evaluation. However, given the nature of complementary medicines and their regulation as foods or dietary supplements internationally, we know that few international regulatory agencies will evaluate the quality, safety and efficacy of ingredients or medicines in a single report. Therefore, we have proposed a range of 'application categories' to allow for a combination of *de novo* data and reports from comparable overseas regulators.

Under the proposed application categorisation scheme, applications in each application category may be assessed in one of three ways:

- **Use of international evaluation reports:** where applicants can provide evaluation report(s) and a complete data dossier for the same ingredient or product from an overseas regulator that meets all minimum data requirements for safety, quality and/or efficacy.
- **Mixed evaluation:** where applicants can provide a mixture of evaluation report(s) from an overseas regulator/s that meets minimum data requirements for safety, quality, and/or efficacy in combination with evidence for *de novo* assessment of the missing parameters.
- **Full *de novo*:** assessment of all parameters (quality, safety, and/or efficacy).

The advantage of this scheme is that it acknowledges the differences in regulatory environments and provides greater flexibility to Australian sponsors to use reports from a range of overseas regulators:

- For those submitting a report from an overseas regulator that meets all minimum data requirements, the evaluation will be streamlined and timeframes will be reduced.
- For those submitting a combination of *de novo* data and an overseas report that meets some of the minimum requirements, the timeframes will be proportionately longer. The quality and scope of the overseas reports will determine the extent to which *de novo* evaluation can be reduced.
- For those submitting a full *de novo* dossier, timeframes will be longer to reflect the additional work-effort required.

The proposed criteria for acceptance of reports from comparable overseas regulators are set out later in this document.

Listed complementary medicines and ingredients

Application categories for complementary medicine ingredients

For any new ingredient to be permitted for use in listed medicines, the applicant must submit a new ingredient application which includes data for **quality and safety** evaluation. Once the ingredient is determined to be safe, it is included in the Permissible Ingredients Determination and may be used in any listed medicine.

We are proposing to create four new application categories (IN1 – IN4) which allow for use of international evaluation reports and *de novo* assessment as described in **Table 1** below.

Table 1: Proposed application categories for new ingredients to be used in listed medicines

Category	Description	Application requirements
IN1	Analysis of safety and quality based on reports from comparable overseas regulators, which meet the minimum data requirements	· Supporting information to demonstrate that report(s) from comparable overseas regulators meet all minimum data requirements · Does not entail evaluation of safety or quality data
IN2	Evaluation of safety based on reports from comparable overseas regulators **and** *de novo* evaluation of quality	· Quality data to be evaluated · Supporting information to demonstrate that all minimum data requirements for safety are met · Does not entail evaluation of safety data as data previously evaluated and approved by comparable overseas regulator
IN3	Evaluation of quality based on international evaluation reports or an accepted monograph **and** *de novo* evaluation of safety	· Safety data to be evaluated · Supporting information to demonstrate that all minimum data requirements for quality are met · Does not entail evaluation of quality data previously evaluated and approved by comparable overseas regulator or covered by accepted monograph
IN4	Full *de novo* evaluation of safety and quality	· Safety and quality data to be evaluated. · Supporting information to demonstrate that all minimum data requirements for safety and quality have been met. · Where the applicant is unable to meet specific technical requirements or applicable guidelines for safety and quality, a robust scientific justification must be made for each deviation from the requirements and/or guidelines

Application categories for the new assessed listed medicines pathway

Although the assessed listed medicines pathway has not yet been established, it is envisaged that sponsors will also be able to submit reports from comparable overseas regulators that satisfy the minimum data requirements for **efficacy** evaluation. As a result, we are proposing to create three application categories (L(A)1 – L(A)3) for the assessed listed medicines pathway that will allow for the use of international evaluation reports or *de novo* assessment, as described in **Table 2**.

Table 2: Proposed application categories for assessed listed medicines

Category	Description	Application requirements
L(A)1	Evaluation of a clone of an existing product, where the only difference is the name and/or flavour, fragrance, printing ink or colour	· Parent medicine must have been fully evaluated (efficacy only) and must comply with current standards · Full access to the parent product dossier must be provided
L(A)2	An application for a new 'generic' medicine[4] OR Evaluation of efficacy based on international evaluation reports	· Supporting information must demonstrate that all minimum data requirements are met · Does not entail evaluation of efficacy data previously evaluated and approved by the TGA or comparable overseas regulator
L(A)3	Full *de novo* evaluation of efficacy An application for a new medicine not covered by L(A)1 or L(A)2, or that is an extension to an existing approved medicine, including: · New therapeutic indications · New strength · New dosage form	· Efficacy data (supporting clinical data) to be evaluated · Supporting information to demonstrate that all minimum data requirements for efficacy have been met · Where the applicant is unable to meet specific technical requirements or applicable guidelines a robust scientific justification must be made for each deviation from the requirements and/or guidelines

[4] A generic product is a medicine that, in comparison to another medicine that is approved or has previously been assessed: has the same quantitative composition of therapeutically active substances, being substances of similar quality to those used in the medicine; has the same pharmaceutical form; is bioequivalent; and has the same safety and efficacy properties.

Application categories for registered complementary medicines

We are proposing that there will be five application categories (RCM1 – RCM5) for applications to register new complementary medicines (**Table 3**). Like the approach taken for ingredient categories outlined in **Table 1** above, these categories provide for the different permutations of **safety, quality and efficacy** reports that may be available from a comparable overseas regulator.

As part of the Complementary Medicines Business Process Reforms in 2015/16, we developed a set of risk based application categories for the assessment of new registered medicines. We have built on these application categories in this consultation paper to accommodate the use of reports from comparable overseas regulators.

Table 3: Proposed application categories for registered complementary medicines

Category	Description	Application requirements
RCM1	Evaluation of a clone of an existing product, where the only difference is the name and/or flavour, fragrance, printing ink or colour	· Parent product must have been fully evaluated (safety, efficacy and quality) · Full access to the parent product dossier must be provided · Evaluation of labels for compliance with RASML[5]
RCM2	Evaluation of safety, quality and efficacy based on reports from comparable overseas regulators **and/or** accepted monograph	· Supporting information must demonstrate that reports from comparable overseas regulators or accepted monograph meet all minimum data requirements · Does not entail evaluation of safety, quality or efficacy data

[5] The Required Advisory Statements for Medicine Labels (RASML) are specified in the

Category	Description	Application requirements
RCM3	An application for a 'generic' medicine OR Evaluation of quality and either safety or efficacy based on reports from comparable overseas regulators **and/or** accepted monograph AND *de novo* evaluation of either safety or efficacy	· Supporting information must demonstrate that reports from comparable overseas regulators or accepted monograph meet all minimum data requirements · May not entail evaluation of data previously evaluated and approved evaluated and approved by the TGA or comparable overseas regulator · Full safety and efficacy data packages may not be required for new generic medicines · Comparative bioavailability studies or a robust scientific justification for its absence should be provided if claims are made to a reference product
RCM4	Evaluation of one of either safety, quality or efficacy based on international evaluation reports **and** *de novo* evaluation of the two remaining parameters OR An application for a new medicine not covered by RCM1 – RCM3 that is a more complex generic medicine, for example: modified-release dose forms OR · New therapeutic indications · New directions for use · Wider target population	· Supporting information must demonstrate that reports from comparable overseas regulators or accepted monograph meet all minimum data requirements · Does not entail evaluation of data previously evaluated and approved by the TGA or comparable overseas regulator · Full safety and efficacy data packages may not be required for new generic medicines · Comparative bioavailability studies or a robust scientific justification for its absence should be provided if claims are made to a reference product

Category	Description	Application requirements
RCM5	New complementary medicines that have not been previously evaluated for quality, safety and efficacy An application for a new medicine not covered by RCM1 – RCM4 that is an extension to an existing approved medicine, including: · New active ingredient · Increase in strength of an active ingredient · New dosage form · Addition of an excipient not currently used in complementary medicines	· Full *de novo* evaluation of safety, quality and efficacy · Supporting information to demonstrate that all minimum data requirements for safety, quality and efficacy have been met · Where the applicant is unable to meet specific technical requirements or applicable guidelines a robust scientific justification must be made for each deviation from the requirements and/or guidelines

Note: the decision maker must take other relevant matters into consideration including the quality, safety, efficacy, presentation and manufacturing standards when making their decision.

Categories for variations of medicines

Variations to registered complementary medicines

The application categories for variations to approved registered complementary medicines have already been established and are summarised in **Table 4**. Further details relating to each category are published in the Australian regulatory guidelines for complementary medicines (ARGCM) regarding:

- whether prior approval is required to make the change
- the relevant section of the *Therapeutic Goods Act 1989* (the Act) that sponsors must apply under
- the relevant change codes
- the application level for the change (as outlined in **Table 4**).

Proposed assessment timeframes for these application categories are provided later in this document.

Table 4: Application categories for variations to registered medicines

Category	Description
C1	Changes identified in the Changes Table as application level C1 Changes classified as **negligible risk** that do not need safety, efficacy and/or quality data. For example, removal of indications or making storage conditions more restrictive.
C2	Changes identified in the Changes Table as application level C2 **Low risk** changes that require evaluation of quality data and do not need safety and/or efficacy data. For example, increasing shelf life or removing the Product Information (PI) where the PI is not required under section 25AA of the Act.
C3	Changes identified in the Changes Table as application level C3 **Low risk** changes to the quality and non-quality aspects of a medicine and requires evaluation of supporting safety and/or efficacy data. For example, adding a claim about 'fast absorption' on the label based on new clinical data.
C4	Changes identified in the Changes Table as application level C4 Includes safety related changes classified as **'moderate risk'**. Applications require evaluation of safety and/or efficacy data (toxicological and/or clinical) to support the proposed changes. For example, new therapeutic indications or new directions for use where 'grouping' applies.

It is important to note that we recently implemented a reform to allow certain changes to registered medicines to be processed as notifications that removes the requirement for pre-approval from the TGA.[6]

Variations to medicines approved through the assessed listed medicines pathway

We are also proposing to develop risk-based application categories for variations to medicines assessed via the assessed listed medicines pathway. Only those changes that have the potential to alter product efficacy will require prior approval by the TGA before the change is made. For example, quality related changes may be self-assessable, whereas changes to add new indications, directions for use or to add claims about product effectiveness may require prior TGA approval following further assessment.

Although this pathway has not yet been established, we propose to develop a changes table similar to the 'registered complementary medicines changes table' which will outline the changes that require approval and those that can occur via notification.[7]

[6] See guidance on the notifications process: requests to vary registered medicines where quality, safety and efficacy are not affected.

[7] See Australian Regulatory Guidelines for Complementary Medicines (ARGCM)(last updated October 2016). Available at: <https://www.tga.gov.au/book-page/5-changes-registered-complementary-medicines>.

- Do you agree with the proposed risk categories for new ingredients and medicines?
- Do you agree with the proposals for application categories to enable use of overseas regulatory reports?

Requirements for pre-market submissions

Minimum data requirements

A set of minimum data requirements will be developed to ensure a consistent standard is applied when complementary medicines and ingredients are evaluated. This will also help ensure the quality of applications received and help us improve assessment timeframes. The minimum data requirements will be based on our experience in evaluating ingredients and products, as well as standards which have been adopted by the TGA and internationally (e.g. International Conference on Harmonisation (ICH), European Medicines Agency (EMA) and European Foods Standards Agency (EFSA)).

Minimum data requirements will be established for safety, quality and efficacy assessment. As described below, all applications will be screened to confirm that they meet minimum data requirements prior to being accepted for evaluation. Meeting the minimum data requirements will not in itself provide an indication of whether a medicine can be considered safe and/or effective. The data requirements will represent the threshold below which a product or ingredient cannot be reasonably evaluated.

The minimum data requirements will also ensure that sponsors using application categories based on overseas assessment reports will be able to address Australian specific requirements.

Note that we will develop minimum data requirements for safety, quality and efficacy assessment and undertake a separate consultation on evidence guidelines for listed medicines.

Use of comparable overseas regulatory reports to support pre-market assessments

The Expert Panel noted that there is a high degree of variation in approaches to the regulation of complementary medicinal products internationally.[8] The main differences are that many other jurisdictions regulate complementary medicines as foods or have food grade manufacturing standards. Currently, applicants are unable to provide reports from comparable overseas regulators as the primary source of evidence for assessment of new complementary medicines or ingredients. They must always be supplemented with additional information.

We are proposing a framework to formalise arrangements for us to accept comparable overseas regulatory reports. The framework is based on a pragmatic approach that allows technical data from a wide range of regulators to be utilised and adapted to meet Australian requirements, provided that a robust set of criteria in relation to how overseas regulators conduct their evaluations are met. This will allow us to use these reports to conduct abridged evaluations that focus on issues that are specific to the Australian regulatory context, such as the product label.

Where overseas regulatory reports are used, we will continue to make the final regulatory decisions, ensuring that quality and safety are not compromised and that the Australian context is taken into account.

[8] Review of Medicines and Medical Devices Regulation, Stage Two – Report on the regulatory frameworks for complementary medicines and advertising of therapeutic goods, pg 17.

Criteria for comparable overseas regulators and their reports

The criteria proposed below will guide our adoption of reports from comparable overseas regulators by enabling identification of evaluations obtained via best practice regulatory approaches. The criteria are designed to be applied through a two-stage process:

- Stage 1: sets out the preliminary criteria that we will use to determine if there is sufficient similarity between the TGA and the overseas regulator.
- Stage 2: sets out the parameters that we will consider to determine the suitability of evaluation reports from overseas regulators and will be considered at the time of submission.

Individual criteria may apply, equally or to varying degrees. We will consider accepting reports from comparable overseas regulators that may not meet all criteria, provided the applicant can provide adequate justification or additional data as required.

Stage 1: Criteria for regulators

Stage 1 criteria describe how closely the overseas regulator's framework aligns with that of the TGA.

Once an overseas regulator has been assessed as both comparable and their assessments appropriate, they will be included as a 'comparable overseas regulator' in a list published on the TGA website. We will develop this list over time as we gain a greater understanding of other regulators and the extent of differences between the overseas approval and the additional information required by us.

Stage 1: Criteria for regulators

- The regulator must be an internationally recognised regulatory authority with an established track record of approving low risk food, chemical or medicinal substances.
- The regulator must have a transparent system for regulatory decision-making. The decision-making framework, risk assessment methodologies and legal responsibilities (including confidentiality and impartiality) should be apparent, and should not conflict with our operating principles.
- The overseas regulator must use internationally accepted scientific standards and guidelines. Our evaluators should be able to readily review the regulatory report in relation to TGA adopted guidelines and approaches.
- We must have, or be able to establish, a relationship with the overseas regulator. The regulator should therefore be able to communicate with us in English.

Stage 2: Criteria for regulatory reports

Stage 2 criteria focus on the specifics of a particular application. Once we have identified an overseas regulator as a suitable source for regulatory reports, the following considerations will be applied to determine whether the proposed use of the comparable overseas regulatory reports can proceed.

It is intended that applicants will use the criteria below at the time of submission to determine the suitability of reports from comparable overseas regulators. These reports can then be submitted with any additional Australian-specific data.

All relevant criteria will need to be addressed to allow reports from comparable overseas regulators to be utilised.

Stage 2: Criteria for regulatory reports
Comparability of the medicine or ingredient
· The formulation, dose, route of administration and/or indications described in the comparable overseas regulatory report(s) must be equivalent to that being applied for.
Nature of the assessment reports
· Reports should be prepared using internationally accepted guidelines and standards consistent with those used by us.[9] · The report(s) must be un-redacted, complete, and written in English or must be a certified translation of the report. · We must be able to use reports from comparable overseas regulators and any supplementary information to publish general information about the safety, quality or efficacy of the medicine, noting that commercial in confidence information will not be disclosed. · The report must be a *de novo* assessment made by an overseas regulator, and present an independent assessment of data provided to that regulator.

Use of reports from comparable overseas regulators

- Are the proposed criteria for determining the suitability of overseas regulators appropriate?
- Are the proposed criteria for determining the suitability of reports from comparable overseas regulators appropriate?

[9] Suitable guidelines and standards include, but are not limited to, the International Council on Harmonisation (ICH) or Organisation for Economic Co-operation and Development (OECD) guidelines; and pharmacopoeial standards such as the European Pharmacopoeia, British Pharmacopoeia and United States Pharmacopeia.

Sources of evidence for *de novo* assessments

The Expert Panel also noted the current range of evidence that is accepted for evaluation of new ingredients for use in complementary medicines is limited and should be expanded.[10] To do so, the Expert Panel proposed that we should consider accepting "internationally recognised papers and articles about ingredients, and recognised monographs, for example, those developed by Health Canada for 'natural health products."[11] Some internationally recognised traditional medicine pharmacopoeia may also be appropriate, noting that those based on a tradition of use do not always include a sufficient demonstration of safety, and additional information may be required of the sponsor. Other non-standard sources of information may include human use data, dietary exposure levels and epidemiological studies.

A framework is proposed below to formalise arrangements for us to accept alternative sources of evidence for *de novo* assessment. This will allow us to use these reports for the assessment of *de novo* parameters (safety, quality and/or efficacy).

Criteria for acceptable sources of evidence for *de novo* assessment

The criteria outlined below will guide our adoption of alternate sources of evidence for *de novo* assessment by enabling the identification of evaluations obtained via best practice regulatory approaches. The criteria are similar, but are not identical to the criteria for comparable overseas regulators and their reports proposed above, and will be applied in a similar way.

The criteria are designed to be applied:

- by us to confirm that there is sufficient similarity between a source of evidence and the minimum data requirements
- by applicants to determine the suitability of an alternate evidence source and will be considered at the time of submission.

All relevant criteria will need to be addressed to allow an alternate source of evidence to be utilised.

[10] Review of Medicines and Medical Devices Regulation – Stage Two, Report on the regulatory frameworks for complementary medicines and advertising of therapeutic goods, pg. 22.
[11] Ibid.

Criteria for acceptable sources of evidence for *de novo* assessment

- The source of evidence must be in English and consistent with the current body of knowledge.
- The source of evidence must be peer reviewed or from reliable publishing sources and any conflicts of interest must be identified.
- The way in which the submitted evidence source is developed must be consistent with internationally recognised guidelines and standards.[12]
- The ingredient, form, dose and route of administration described in the source of evidence must be equivalent to that being applied for.

A list of acceptable sources of evidence will be published on the TGA website for use by applicants. This will not be an exhaustive list however, as we will also accept additional sources of evidence that meet the above criteria at the time of submission. Acceptable source of evidence include:

- Herbal monographs, scientific monographs, and adverse event databases that meet the minimum data requirements for safety.
- Pharmacopoeial monographs that meet the minimum data requirements for quality.

For example, we have determined that the Korean Pharmacopoeia, Japanese Pharmacopoeia and World Health Organisation monographs will meet the proposed criteria and the minimum data requirements for quality. This is because the test criteria, limits and specifications are similar to or the same as those which exist in TGA default standards.[13]

Sources of evidence for *de novo* assessment

- Is the proposed process for identifying alternate sources of evidence for *de novo* assessments appropriate?
- Are the individual criteria appropriate?
- On the basis of the above criteria, please propose other sources of evidence that you would like considered as acceptable for *de novo* assessment.

[12] Note that the evidence must cover the range of tests and minimum data requirements for listed medicine ingredients in accordance with the internationally accepted guidelines and pharmacopoeial standards. Sponsors must be able to justify why and how the evidence source meets the minimum data requirements.
[13] The default standards specified in the *Therapeutic Goods Act 1989* are the British Pharmacopoeia (BP), United States Pharmacopoeia (USP), and the European Pharmacopoeia (Ph.Eur).

Business processes for pre-market assessments

Proposed pre-market assessment process

We are proposing to introduce a standardised pre-market assessment process to help us introduce legislated assessment timeframes for assessment of applications for new ingredients proposed for use in listed medicines, the assessed listed medicines pathway and the registered medicines pathway.

It is proposed that **all** applications that involve pre-market assessment will follow similar processes, with lower application levels having shorter assessment timeframes due to the reduction in information to be evaluated.[14] The approach shown in **Figure 1** below is similar to the current process for registered complementary and over-the-counter medicine applications. We are proposing that this process will be supported by an application fee payable at the time of submission and an evaluation fee to be paid at the screening phase once an application is determined to be effective.

Figure1: Proposed pre-market assessment process

Pre-submission meeting

Pre-submission meetings are already offered to applicants and are strongly encouraged. They provide an opportunity for applicants to seek clarification of our requirements and to revise the approach to their application. They will also assist us to process applications within the legislated timeframes.

The following principle will apply:

- There will be no additional costs for a pre-submission meeting, as costs associated with these meeting will be covered by the application fee.

Submission phase

The submission phase will commence when a sponsor makes an application seeking approval of a new (or changed) medicine or a new ingredient. The applicant will determine which application category is appropriate based on the data requirements of the applicable category. The application fee must be paid during this phase.

Screening phase

The screening phase is a quality assurance process to check whether an application is 'effective', i.e. that the application meets the minimum requirements (i.e. correct application type, data and application fee) to proceed to evaluation.

[14] Note that medicines listed through the 'standard' listing pathway (i.e. that only use permitted indications) will continue to be listed on the basis of self-assessment / certification by the applicant.

The following principles will apply:

- If the application is determined to be effective, the application will be accepted for evaluation and the evaluation fee will become due and payable.
- Ineffective applications that do not meet the minimum data requirements will not be accepted for evaluation and the application fee will be forfeited.

Evaluation phase

In the evaluation phase, the data submitted in support of the application will be assessed.

The evaluation phase covers:

- Evaluation of the information provided by the sponsor in accordance with the requirements of the selected application category, and where required, referral to an advisory committee.
- Requests for information (RFI) to clarify specific aspects of the application.
- Documentation of findings and a recommendation for approval or rejection for the delegate's consideration.

The following principles will apply:

- We are proposing that legislated timeframes will only commence once an application has been accepted for evaluation and following payment of the evaluation fee.
- Timeframes apply to working days only and exclude public holidays, weekends, and time taken by the applicant to provide responses to formal RFIs (i.e. the 'clock' will stop).
- Once the evaluation has commenced, the sponsor will not be able to make changes to the application or submit additional information unless requested to do so by us.

Requests for information

Where there is insufficient information for the evaluator to assess the medicine or ingredient, the evaluator may seek clarification or additional information. If we request information, the clock will stop from the time we make the request until we receive a response from the applicant. The evaluation will not resume until complete responses to RFIs have been provided.

The following principles will apply:

- We are proposing to limit requests for information to a single round.
- There will be standard timeframes for applicants to respond to RFI's.[15] Where a sponsor fails to answer a RFI within the required timeframe, we will proceed to evaluate the application without the additional data. This may result in the rejection of the application.
- Evaluators can also seek clarification of minor issues on an informal basis. The clock will not stop in these circumstances.
- The RFI process is not intended to provide sponsors with an opportunity to supply information that should have been included in the original application.

[15] The standard response time for a sponsor to respond to a request for information will be 20 working days.

Decision phase

In making a decision on an application for a complementary medicine or ingredient, the delegate takes into consideration the evaluation report, any advice given by an advisory committee and any subsequent comment provided by the applicant.

The applicant will be advised of the decision in writing. If the decision is to reject the application, the letter will provide the reasons for the decision. If the decision is to approve the application, the standard and specific conditions of registration will be provided.

The following principle will apply:

- It is proposed that legislated timeframes will stop at the point that the delegate makes a decision to approve or reject the application and advises the applicant in writing.

Implementation phase

This step involves administrative matters, including entry of details into the ARTG in the case of products evaluated under the assessed listed medicines pathway or the registered complementary medicines pathway. For new ingredients, this will involve inclusion of the ingredient in the Permitted Ingredients Determination and finalisation of a compositional guideline.

Pre-market assessment process

- Do you support the proposed assessment process and principles as outlined above?

Proposed legislated assessment timeframes

The Australian Government has agreed to the development of legislated timeframes for complementary medicine pre-market assessments. We are proposing to develop legislated assessment timeframes for the:

- Assessment of new ingredients for use in listed medicinal products.
- Assessment of medicinal products listed under the new assessed listed medicines pathway.
- Assessment of medicinal products under the registered medicines pathway.[16]

Implementing legislated timeframes will improve predictability, and thereby allow sponsors to better plan the roll out of new products to the market. The proposed timeframes align with the risk-based application categories as outlined in Table 1, 2 and 3 above.

[16] The publication of compositional guidelines following approval of new ingredients for use in listed medicines is not an administrative decision under the *Therapeutic Goods Act 1989*. We will consider target timeframes for publication of compositional guidelines in the context of implementation of Recommendation Fifty of the MMDR. See Review of Medicines and Medical Devices Regulation – Stage Two, Report on the regulatory frameworks for complementary medicines and advertising of therapeutic goods, pg. 45.

The proposed legislated timeframes for ingredient assessments, assessed listed medicines and registered complementary medicines is shown in **Table 5** below.

Table 5: Application categories and proposed legislated assessment timeframes (in working days) for complementary medicine assessment pathways

	Application level	Screening[17]	Total evaluation time
Complementary medicine ingredients (refer to Table 1)	IN1	5	70
	IN2	20	120
	IN3	20	150
	IN4	25	180
Assessed listed medicines (refer to Table 2)	L(A)1	5	45
	L(A)2	10	60
	L(A)3	15	150
Registered complementary medicines (refer to Table 3)	RCM1	15	45
	RCM2	15	90
	RCM3	20	150
	RCM4	20	180
	RCM5	25	210
Variations to registered medicines (refer to Table 4)	C1	1	20
	C2	2	64
	C3	2	120
	C4	5	170

Legislated timeframes

- Are the timeframes for the individual application categories appropriate?

[17] Please note that the screening phase is not included in the legislated timeframe.

Proposed new fee structure to support application categorisation

Applicants seeking evaluation of new ingredients and registered complementary medicines are currently required to self-determine the appropriate **evaluation fee** based on the total page count of safety data in their application. Administrative and quality data are currently excluded from the page count. However, the number of pages does not take account of the relevance or complexity of the information and so is not an accurate reflection of the effort or risk associated with the assessment. As noted by the Expert Panel, "there is a financial disincentive to the sponsor providing a detailed submission at the start of the application."[18]

We propose to introduce a new fee structure that is commensurate with the amount of work required and that aligns our fees to the cost of providing evaluation services. The new structure will complement the pre-market assessment process and legislated timeframes outlined above. The Expert Panel noted that revision of the fee structure to move away from a page count based structure may also improve application quality, with consequent improvements to assessment timeframes.[19]

Approach to fee calculation

Our approach to the development of the proposed new fee structure is to apply fees that reflect the level of risk of a new or varied medicine and therefore the level of scrutiny that the application receives by us. The proposed structure will also ensure that our fees are aligned with the costs of undertaking evaluation of the application.

We are proposing the following:

- **Application fees** will cover the administrative costs associated with an application and are proposed for all application types (note that there are currently no separate application fees for ingredient assessments). Application fees will be payable in the submission phase.
- The work associated with pre-submission will be reflected in the application fee.
- To facilitate the submission of high quality applications, a non-refundable application fee is payable when the application is lodged with us.
- **Evaluation fees** will cover the cost of assessing the supporting information in an application. The evaluation fee is payable when the applicant has been notified that we have accepted the application for evaluation (see screening phase above).

The fees have been designed to reflect the amount of work required to complete the relevant applications and evaluations, based on the circumstances of the different application categories and the complexity of documentation associated with them. For example, the fees for an RCM 1 application will be commensurately lower than those for a more complex RCM 5 application.

Given the degree of change associated with the introduction of the proposed new risk-based application categories; in particular the uncertainty around the complexity and work effort involved for assessments using reports from comparable overseas regulators and the new assessed listed medicines pathway, we are proposing a staged approach to the introduction of the new fee structure.

[18] Review of Medicines and Medical Devices Regulation, Stage Two, Report on the regulatory frameworks for complementary medicines and advertising of therapeutic goods – , pg 31.
[19] Ibid, pg 32.

During the first stage, the same fees will apply for some application categories with different risk levels, however these application categories will still differ in the amount and type of information we need to assess and the applicable legislated timeframe. For example, IN3 and IN4 applications will have the same fee, but IN3 will have shorter timeframes and lower data requirements. The same fee is required for these applications given that assessments based on reports from comparable overseas regulators are a new process that will not necessarily result in a reduction in work effort for the TGA.

During the second stage, information obtained about the assessment process and the work effort associated with the different application categories will be used to inform a review of fees to ensure appropriate cost recovery for the sector.

Changes to fees and charges will be consistent with cost recovery principles. A Cost Recovery Implementation Statement detailing the new fee structure will be released later in 2017.

The proposed fee structure for each assessment pathway is provided in **Table 6**, **7, 8** and **9** below. **Please note that the proposed fees are an initial estimate only. They will require further assessment before being finalised.**

Proposed fees for assessment of new ingredients

The proposed application and evaluation fees for assessment of new complementary medicine ingredients are set out in **Table 6**. While there are four application categories for new ingredients, there are only two fee amounts. Applications submitted under IN1 or IN2 will have the same fee ($15,050) but the assessment timeframes will be 70 days and 120 days respectively. Applications submitted under IN 3 or IN 4 will also have the same fee ($25,670) but the assessment timeframes will be 150 days and 180 days respectively.

Table 6: Proposed fees for assessment of new ingredients

Application category	Application Fee	Evaluation Fee	Total Fee
IN1	$1050	$14,000	**$15,050**
IN2			
IN3	$2770	$22,900	**$25,670**
IN4			

Proposed fees for assessment of listed assessed medicines

The proposed application and evaluation fees for an assessed listed medicine are set out in **Table 7**. The total fee for an application submitted under L(A) 1 will be $2070, with a total evaluation time of 45 days. Given our uncertainty over the relative complexity of assessments of applications submitted under L(A) 2 and L(A)3 they will have the same fee, but will have assessment timeframes of 60 days and 150 days respectively.

Table 7: Proposed fees for assessment of listed assessed medicines

Application category	Application Fee	Evaluation Fee	Total Fee
L(A)1	$430	$1640	**$2070**
L(A)2	$ 1760	$13,400	**$15,160**
L(A)3			

Proposed fees for assessment of new registered complementary medicines

The proposed application and evaluation fees for registered complementary medicines are set out in **Table 8**. The approach is the same as for new ingredient assessments and assessments of listed assessed medicines, with the total fee for an application submitted under RCM2 and RCM3 being the same ($22,410), but having assessment timeframes of 90 days and 150 days respectively.

Table 8: Proposed fees for assessment of new registered complementary medicines

Application category	Application Fee	Evaluation Fee	Total Fee
RCM1	$530	$3060	**$3590**
RCM2	$1910	$20,500	**$22,410**
RCM3			
RCM4	$2530	$27,800	**$30,330**
RCM5	$2770	$35,500	**$38,270**

Proposed fees for assessment of changes to new registered complementary medicines

Table 9 below sets out the proposed fees for assessment of changes to new registered complementary medicines. These fees do not follow the same approach as outlined above. Each application category has a separate application and evaluation fee which reflects our confidence in the work effort required to conduct these assessments.

Table 9: Proposed fees for assessment of changes to new registered complementary medicines

Application category	Application Fee	Evaluation Fee	Total Fee
C1	$1380		**$1380**
C2	$730	$3960	**$4690**
C3	$780	$6190	**$6970**
C4	$790	$9160	**$9950**

Notes:

- C1 applications do not involve assessment of data and will only have an application fee
- Where evaluation of data is not required for a C2 application, an application fee equivalent to C1 application fee will apply.

Proposed fees

- We wish to obtain your feedback regarding the development of the new fee structure in the context of legislated assessment timeframes that will streamline approval processes. We seek your views on the proposed fees and any other details or requirements that you believe should be included.

Enhanced post-market compliance monitoring scheme for listed medicines

Consistent with current arrangements, low risk listed medicines will not be evaluated by us before they are listed on the ARTG. Rather, the sponsor will continue to self-assess their medicine and certify that their medicine meets all requirements for listing. We review a proportion of listed medicines post-market to check compliance against relevant regulatory requirements and confirm the ongoing quality, safety and efficacy of the product. Medicines may be randomly selected or targeted for a review.

Despite the number of compliance reviews having increased in recent years from 212 in 2014-15 to 551 in 2016-17, the level of non-compliance has remained high. Between July 2015 and June 2016, only 20% of reviewed listed medicines that were subject to a random review were found to be compliant against selected regulatory requirements and 80% required the sponsor to address identified compliance breaches.[20]

Timely access to listed medicines needs to be balanced with a comprehensive post-market compliance monitoring scheme that provides a level of assurance of safety, quality and efficacy of these products so that confidence in the TGA's regulatory framework is maintained. In order to address the high rates of non-compliance, we are proposing to enhance the existing post-market monitoring processes through three strategies discussed below.

Greater targeting of non-compliant sponsors

The Expert Panel noted that high levels of non-compliance may be linked to 'the small chance of being reviewed and insufficient penalties for non-compliance'.[21] We are aware, for example, that approximately 10% of the time, sponsors withdraw their product from the ARTG following a request from us to provide information for a compliance review. [22] The sponsor can then relist the medicine and avoid a possible negative finding from a compliance review.

We propose to target repeated non-compliant behaviours and remove the incentive to withdraw and re-list a product to avoid a compliance review. Where appropriate we will use the full range of enforcement sanctions as described below.

Improved identification of non-compliant behaviours

We currently gather compliance data that assists us to identify actions and behaviours that are likely to lead to a high risk of non-compliance. We are proposing to build upon these data to target sponsors who:

- Routinely cancel products from the ARTG prior to completion of compliance reviews
- Have a significant history of non-compliant medicines listed on the ARTG.

We propose to use this information to select multiple listed medicines from the same sponsor for post-market compliance review until the sponsor's behaviours and actions improve.

[20] TGA, Performance statistics report: July 2015 to June 2016 (last updated September 2016). Available at: <https://www.tga.gov.au/performance-statistics-report-july-2015-june-2016>.
[21] Review of Medicines and Medical Devices Regulation, Stage Two – Report on the regulatory frameworks for complementary medicines and advertising of therapeutic goods, pg. 42.
[22] TGA internal data – based on data for the period July 2016 to June 2017.

Enforcing penalties for repeat non-compliance

In appropriate cases, sponsor behaviour could more readily be influenced by enforcing appropriate penalties for non-compliance.

We recently published a consultation paper, 'Enhancing sanctions and penalties in the *Therapeutic Goods Act 1989*', which closed on 31 May 2017. Given the paper's focus on enhanced penalties, we will look to use stronger penalties for sponsors who demonstrate a clear intent to circumvent their obligations under the Act. For example, use of infringement notices could be based on a 'repeat offenders policy' e.g. if the behaviour occurred by the same sponsor three times. Infringement notices could also be issued to discourage the incentive to withdraw and re-list a product to avoid a compliance review.

Improving transparency about compliance review outcomes

We currently publish limited information about products that have been cancelled from the ARTG following compliance reviews. While this information provides a useful overview of compliance outcomes, we recognise that this information can be expanded upon to provide more detailed information, in plain language about the reasons for the cancellation. Increasing transparency about compliance outcomes may raise awareness of non-compliance, including repeat offenders and thereby deter non-compliant behaviours and provide greater protection for consumers.

Additional information that may be released includes:

- the compliance issues that were identified during the review e.g. specific claims that were not supported by the evidence provided
- what actions the sponsor took e.g. removal of unsupported claims to bring a product into compliance
- if a product is cancelled, more detail about the reasons why a product was cancelled, e.g. the sponsor was unable to provide evidence to support their claims.

In considering the extent of information to be released, we will have regard to the need to balance consumer protection with the industry's need to protect commercial information and procedural fairness.

Education and resources for product sponsors

In order to foster and maintain compliant behaviours and practices by medicine sponsors we are proposing to work with industry to develop educational tools and resources and improve our regulatory guidance material so that sponsors can better understand their regulatory obligations.

The TGA has recently launched SME Assist to support Small and Medium sized Enterprises (SME's) understand their regulatory and legislative obligations. More information regarding this initiative can be found at the SME Assist Hub. We propose to introduce resources that are specific for complementary medicines sponsors as discussed below.

Educational resources

In 2016 we created a landing page 'Compliance and education for listed medicines' on the TGA website to provide sponsors with a better understanding of common and problematic compliance issues and how they can be avoided. It also contains information about all current and future reviews priorities to give sponsors better insight and forewarning to encourage voluntary compliance.

We will also work with industry to expand the range, type, messaging and format of guidance material available to encourage compliance.

Sponsor education and training

We are proposing to deliver 'roadshow' style training to ensure sponsors understand their regulatory obligations and our regulatory compliance framework. This will be particularly important following implementation of the recommendations arising from the MMDR review. The aim of the training will be to reduce unwitting or unintentional non-compliances that may arise due to lack of knowledge or understanding and to foster and acknowledge compliant behaviours.

Regular sponsor training days could also be held, where there is a clear interest from industry, to provide education about common and problematic compliance issues.

Online training

Knowledge of our regulatory requirements could also be enhanced through an online training portal that could be a requirement for applicants for listed medicines. Completion of online training could be used as a prerequisite for obtaining access to the Electronic Listing Facility (ELF), or on an annual basis as a pre-condition of making a listing application or medicine.

Sponsors that have intentionally and repeatedly contravened the Act would have to successfully repeat the online training to demonstrate that they understand their obligations under the Act to apply to list a new medicine in the Register.

Data gathering and intelligence

In addressing non-compliance it is imperative to understand why and how the non-compliances are occurring. It is therefore essential to have good data or 'intelligence' to be able to analyse and understand the patterns of non-compliance and greatest areas of risk.

In enhancing our post-market monitoring scheme, we are working to integrate more data about non-compliant behaviour, including improving collaboration with overseas regulators of therapeutic goods. This approach will assist us to more readily identify patterns of non-compliance, target education towards the areas of greatest need and develop strategies to target emerging compliance risks.

Data linkages - permitted indications

Subject to passage of supporting legislation, from January 2018, sponsors of all new listed medicines will be required to select their product indications from the list of 'permitted indications' and the 'free-text field' will be turned off.[23] Sponsors of existing listed medicines will be required re-list their products using permitted indications by January 2021. This reform will allow us to link individual permitted indications and/or categories of indications with other relevant information (e.g. previous compliance outcomes, product ingredients etc.) to identify non-compliance trends e.g. where the use of a permitted indication for a certain ingredient was not supported by evidence. This data will be used to plan future targeted reviews to bring specific categories of product back into compliance.

Enhanced post-market monitoring scheme

- Do you agree with the proposed approaches to target repeat offenders? If not, please outline other approaches that could be used to target this behaviour?
- Is the proposal to publish more information about compliance review outcomes appropriate?
- Do you have any views on the educative tools, including methods of delivery and locations of roadshows, to improve rates of compliance?

Implementation

Phased implementation of the new business processes

Following completion of consultation and before implementing any changes to the complementary medicines business processes, the following will occur.

- Consultation on minimum data requirements.
- Development of a number of forms and guidelines including:
    - § application form(s) that clearly specify minimum data requirements for each category of application
    - § updates to regulatory guidelines including the Australian Regulatory Guidelines for Complementary Medicines to include guidance regarding use of reports from comparable overseas regulators
    - § tool(s) such as decision trees to assist sponsors to determine the appropriate application category for their medicine.
- Development of a Cost Recovery Impact Statement to support the revised complementary medicines fee structure. Consistent with cost recovery arrangements, the proposed fees will be reviewed at a later stage to ensure appropriate cost recovery.

[23] This reform will implement Recommendation Thirty-eight of the MMDR review. More information about the permitted indications reform is available on the TGA website. See: <https://www.tga.gov.au/complementary-medicines-reforms>.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Complementary and OTC Medicines Branch	August 2017

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
https://www.tga.gov.au

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