ASMI Response to the Review of Medicines and Medical Devices Regulation

Reforms to the regulatory framework for complementary medicines

Assessment pathways

March 2017

About ASMI

ASMI is the peak body representing companies involved in the manufacture and distribution of consumer health care products (non-prescription medicines) in Australia. ASMI also represents related businesses providing support services to manufacturers, including advertising, public relations, legal, statistical and regulatory consultants. A full list of ASMI members is available on the ASMI website.

Introduction

ASMI is welcoming of regulatory reform initiatives designed to improve the transparency, productivity, and confidence in the complementary medicines sector. In this regard, ASMI is supportive of the majority of the proposed recommendations and appreciates the opportunity to contribute to the development of the new regulatory model.

It should be noted that all of the comments in this consultation response are provided without visibility of the overarching regulatory framework. The complete MMDR reforms project has many intersections within the medicines framework, and the full outcome of the current consultation can only be understood in the context of the whole. Changes to advertising, low risk medicines and permitted indications will have a particular impact on the suitability of the proposals within this consultation. While ASMI will respond to each consultation accordingly, ASMI reserves its final position and support until a review of the intersection of the completed consultations is made available for stakeholder consideration and input prior to any legislative changes being put forward.

ASMI requests that the TGA provide a clear overview of how they intend to address each of the Government responses to the Expert Review recommendations. The current approach is segmented, and stakeholders do not have transparency of the projected final product. ASMI also notes that these changes, along with associated reforms that are not specifically within the complementary medicines space, are likely to have a marked impact on the entire regulatory framework and this will come with business impacts and costs. ASMI therefore requests that a full regulatory impact statement is provided to address these concerns, particularly where the TGA proposal does not appear to align with the intention of the Expert Review recommendations and Government response.

ASMI also emphasises the importance of maintaining consistency of the medicines framework across the various risk classes. Listed medicines are regulated by the TGA as part of the overall medicines and medical devices framework, and as such, it is essential that all reforms maintain consistency with the overall framework, do not create consumer confusion in relation to other product types, do not introduce unnecessary complexity, and do not introduce excessive regulatory burden.

Executive Summary

Assessment Pathways

ASMI supports that a third assessment pathway for complementary medicines could be beneficial, however ASMI does not support the proposed definitions provided for each of the pathways or the outlined evidence requirements. The recommendation for a third pathway was described as providing sponsors additional flexibility to access higher level indications than are currently appropriate for listed medicines. The proposal outlined is inconsistent with this recommendation and introduces further barriers rather than flexibility.

ASMI does not support the restriction of products currently appropriate as listed medicines or registered complementary medicines through the introduction of new definitions.

- The presentation and definition of each of the three pathways within the consultation paper is effectively creating a new standard for all complementary medicine types rather than introducing additional flexibility.

- Listed medicines that are currently appropriate as listed medicines should remain in this pathway, similarly registered complementary medicines should not have new and higher expectations introduced

ASMI does not support the proposed evidence requirements as these are also inconsistent with the recommendation, introduce a disproportionate evidence requirement for each assessment pathway, and do not include some flexibility to accommodate the wide range of complementary medicines.

- The minimum data requirements should be consistent with the equivalent medicine risk levels. Therefore registered complementary medicines should not be held to a higher evidence standard than equivalent registered medicines. Instead this should be used as a guide to an upper level and evidence requirements for the new pathway and listed medicines should be determined respective to this and their associated risk.

- There are a range of products that are suitable to be registered as complementary medicines, however there is variability in the actual risk of each of these products dependent on the ingredients and indications. The evidence and risk framework needs to provide sufficient nuance that all registered complementary medicines are not designated as 'high' risk, or treated akin to medicines requiring the intervention of a healthcare practitioner.

- The consultation paper acknowledges that complementary medicines can encompass a wide range of products that have varying sources of evidence. This complexity needs to be accepted and reflected in the evidence requirements and must accommodate the broad range of products and ingredients, their established history of safe and effective use, the complexity of formulation types, and whether requirements, such as bioequivalence, will provide an attainable and useful standard.

ASMI also holds concerns regarding how the proposed new pathway will fit within the existing two-tiered system for the regulation of medicines. While ASMI firmly believes in the value of a risk-based hierarchy, the proposed model is difficult to define and adds undue complexity to the regulatory

framework by appearing to create a complementary medicines specific risk definition within the existing medicines classification.

The TGA needs to be very clear whether their intention is to move towards a genuine three-tiered system for the regulation of medicines, or whether the new pathway will be positioned as a subset of either the existing listed or registered tiers. This intention needs to be publicly communicated, with an opportunity for further input to be provided.

ASMI also notes that the MMDR recommendation outlines that these pathways must be suitable for complementary medicines and other listed medicinal products for supply in Australia. This conflicts with the approach of the current consultation which omits other non-complementary listed medicinal products from the scope of discussion; ASMI considers this to be inappropriate. Consistency needs to be maintained across the entire medicinal products framework rather than introducing further segmentation and complexity.

Further clarity and consultation is required regarding the intended impacts on the export only listing pathway.

Permitted Indications

ASMI agree with the establishment of a permitted indications list from which indications must exclusively be drawn for listed medicines. ASMI is prepared to support the removal of free text from the listing system, however this support is conditional on the following provisions. The permitted indications list must be:

- Comprehensive;
- Easy to use;
- Easy to amend/add new indications/conditions (providing these meet the definition of listed medicines);
- Only assessed in terms of the validity for listed medicines, rather than a consideration of the efficacy.

Further to this, the Permitted indications list should not introduce new limitations for listed medicines or regulatory controls that are not aligned with the MMDR recommendations. ASMI holds the following views:

- Restricted representations should be available for listed medicines where a public health benefit is identified supporting the ready access to particular ingredients/indications. Current exemptions for restricted representations should not be removed from listed medicines as these have already been assessed as meeting public interest criteria.
- Prevention of vitamin/mineral dietary deficiency related health consequence, or sunscreens for the prevention of skin cancer have a valid place as low risk medicinal products and should not be removed from the current permitted indications framework.

- Biomarker indications should not be categorically removed from permitted indications where the target population and the evidence is consistent with a listed medicinal product i.e. health maintenance.

ASMI agrees with the proposed mechanism for including Permitted Indications in the listing portal if the preceding principles are followed. Option 2 'Core permitted indications which can be modified with pre-approved qualifiers' appears to provide the greatest capacity for manageability and usability.

ASMI supports the provision of transparency for non-permitted indications, however this should be provided through guidance documents rather than in the form of a further legislative instrument.

Claimer

ASMI is opposed to the introduction of a product 'claimer'. The objective of the reforms is to increase transparency for health professionals and consumers about the evidence base for health claims, however this proposal is likely to increase confusion and complexity rather than contribute to transparency as per the recommendations.

ASMI asserts that this proposal will create a conflict in regulation, advertising and consumer expectations across the entire medicines framework. Enabling a 'claimer' that is only available to pre-market assessed complementary medicines:

- Contributes to consumer difficulty in making suitable comparisons between different medicine types
- Will likely create consumer confusion regarding the efficacy of products not carrying such a claimer, such as sunscreens, OTC and prescription medicines.
- Increases the risk of vulnerable populations not choosing the most appropriate medicine
- Is inconsistent with the advertising principle of TGA not allowing endorsement of products while potentially damaging consumer perceptions of the impartiality of the TGA.
- Undermines the medicines framework, creating an unlevel playing field and inconsistency between complementary, OTC and prescription medicines.

The only way that the claimer will increase transparency and be consistent with the recommendation is if it is available to all products that have had their evidence assessed by the TGA. This includes pre-market and post-market assessment of evidence, and all medicinal types from listed products through to prescription medicines. It should be noted, however, that this would not be consistent with the principles of a robust and credible regulatory system and likely damage international market harmonisation and export.

The Government response acknowledged both the need to carefully consider the design and use of these statements as well as the importance of consumer education to communicate the different levels of regulation. ASMI believes that unless the representation for the new pathway is simply in the form of a product identifier, akin to an AUST L or AUST R, that any presentation will introduce

unintended and adverse consequences. Further to this, an effective consumer education campaign is pivotal to achieving any possible benefit from such a proposed mechanism, however consumer understanding of the existing medicines framework is already poorly realised. This proposal will further increase the complexity of the regulatory environment while introducing labelling that is more likely to mislead than not.

ASMI proposes that instead of introducing a 'claimer' the TGA undertakes a robust consumer education campaign that informs consumers about the new pathway, along with the entire medicines framework. This provides mechanisms for communicating the evidence base without the high risk of introducing an easily misinterpreted statement.

Competitiveness and Incentives

ASMI supports the introduction of market exclusivity and data protection mechanisms to improve competitiveness in the Australian complementary medicines industry, however there is currently insufficient clarity regarding the application of the mechanisms and how these mechanisms will be enforced. As a general position, ASMI proposes three years as a suitable protection period for both ingredients and indications.

- Two years is insufficient for new substances to provide an adequate incentive, however ASMI understands that this would be applied through a flag in the listing system that requests documented authorisation to use the substance, much in the same way as proprietary ingredients currently function.
- A more detailed modelling of how data protection for evidence would work is needed to ensure that the mechanisms will be functional, but also to determine what protection period is going to be optimum.

Transition

ASMI supports a three year transition time, however it is not reasonable to commence the transition period without all mechanisms available or without clarity regarding how the entire regulatory reform project is expected to intersect. A streamlined and effective transition is dependent on all mechanisms being available at the start of the transition period, particularly if there is an expectation that any current listed medicines will need to transition to the new pathway.

ASMI also emphasises the importance of having visibility of the complete regulatory reforms project, including low risk medicines, the permitted indications list, and changes to advertising, prior to implementation. The ability to review the complete regulatory picture, and provide any final contributions, will help to support a comprehensive framework for low risk and complementary medicines and facilitate a smooth transition.

Assessment pathways for complementary medicines

A risk-based hierarchy for therapeutic indications
3.1 Do you agree with the proposed indication hierarchy and the criteria proposed to distinguish the three medicine pathways?

In principle, ASMI agrees with a risk-based hierarchy of indications, and these indications drawing a general parallel to the regulatory pathway, however it should be noted that factors outside of the indication, such as ingredients and route of administration, are also critical in establishing the overall product risk, and these may vary independently of the product indication. ASMI seeks further clarification of the alignment between the current two-tiered regulatory framework and the proposed three-tiered regulatory framework. A clear matrix should be developed and published for consultation prior to moving forward with the implementation.

It should also be noted that potential or identified benefit is a pivotal component of the Australian medicine regulation framework, with one of the functions of the TGA to regulate products on an assessment of risks versus benefits. Therefore, while ASMI does generally support that the indications would be categorised into three levels of risk, low, intermediate and high, corresponding to the listing pathway, the new pathway and the registration pathway respectively, a certain degree of flexibility and pragmatism needs to be maintained.

ASMI does hold concerns over the proposed eligibility criteria for the three assessment pathways, and believes that further work is needed to make these pathways constructive, accessible and useful.

Three key concerns have been identified which are suggested to distinguish between the current Listed pathway and the New pathway:

1. Scope: The proposed reduction from the currently available permitted indications for listed medicines, with a subset to be designated as requiring pre-market assessment. ASMI supports the removal of free text and improving compliance for listed medicines, however the TGA proposal is suggesting a significant reduction from the previously accepted Coded indications. Instead of increasing flexibility, as per the recommendations, this will increase the regulatory burden for many products that are currently consistent with the principles of listed medicines.
2. Terminology: A distinction between indications for each pathway is defined by the following phrases "*prevention or alleviation* of a non-serious form of disease of condition" for the New Pathway and can "*imply a benefit for* non-serious forms of a disease or condition" for Listed Medicines. It is not clear how these are distinct as 'implying a benefit' has the same meaning and core intent as 'prevention or alleviation'. Therefore clarity is required over whether the distinction is in the actual terminology or the intent of the indications. This has been an ongoing cause of confusion within the complementary medicines regulations and the current reforms should be used as an opportunity to improve clarity.
3. Restricted representations: The New Pathway medicines can refer to restricted representations, and it is proposed that the currently approved restricted representations will no longer be suitable for listed medicines. Abandoning the public interest criteria for listed complementary medicines to carry approved restricted representations needs to be carefully considered. Requiring products to meet the proposed evidence criteria for the new pathway before it can refer to a restricted representation may not necessarily equate to the best interest of the public.

These need to be considered within the continuum of Government decisions to allow for food fortification and health claims, along with other low risk, non-complementary therapeutic goods such as sunscreens.

Further to this, ASMI does not support that identifying a vulnerable population in the indication automatically requires a product to be assessed through the new pathway or registered. The target population does not in its own right determine the risk level of a product. For instance, nappy rash creams should not be required to transition to the new pathway simply because the target population are infants. While this criteria is relevant in determining the risk category of the finished product, this is secondary to the context and the indications for the product.

Low level indications

ASMI supports that "low risk indications are consistent with what is appropriate for listed complementary medicines under the current framework and would include both specific and non-specific indications based on a tradition of use or scientific evidence."

ASMI agrees that if delaying medical advice or treatment for a condition may have adverse health consequences for the patient then it is not a suitable indication for the low level pathway.

ASMI proposes that the definition for a low level indication should be amended to improve the consistency and transparency of the regulatory system, and avoid the vagueness of "serious form of a disease or condition" as referenced in the Therapeutic Goods Advertising Code, Part 2 of Appendix 6. ASMI proposes that low level indications can refer to general health maintenance, enhancement, prevention of dietary deficiency or those that imply a benefit for a self-manageable or self-diagnosable and self-limiting condition, where a delay in medical intervention is not detrimental to the consumer.

Intermediate level indications

ASMI holds significant concerns regarding the positioning of the new category. Further consideration is needed into how this category will fit between the existing listing and registration pathways and how the risk categorisation for the new pathway is defined.

The intermediate pathway has been described as follows:

> "Intermediate level indications will include references to prevention or alleviation of non-serious forms of a disease, condition, ailment, defect or injury. Although the diseases captured by these therapeutic uses will generally be naturally self-limiting, self-diagnosable and/or self-manageable, medicines carrying these indications may present higher risk to consumers than low level indications.
>
> Intermediate indications are generally more definitive, relate to more serious health conditions and incorrect use might, for example, lead to a delay in seeking medical treatment and adverse consequences for the consumer. Allowing such medicines to be supplied without being individually assessed for efficacy would undermine the TGA's risk-based regulatory framework"

By the very nature of the description this category does not pragmatically exist, since a condition that is self-limiting is not feasibly also likely to result in adverse consequences should the consumer delay in seeking treatment. It is difficult to understand the true difference between the indications which are considered appropriate for Listed Medicines vs the New Pathway. Both include indications for non-serious forms of disease or conditions, and those which are self-diagnosable, self-manageable and self-limiting.

ASMI proposes that the definition is revised to avoid confusion regarding what is a serious or non-serious form of a disease or condition. ASMI suggests that an intermediate level indication will include references to the prevention or alleviation of a self-manageable or self-diagnosable and self-limiting disease, condition, ailment, defect or injury, where a delay in medical intervention is not likely to result in serious adverse consequences for the consumer.

<u>High level indications</u>

Although this has been presented as the current registration pathway with no changes, there does appear to be a variation to the definition of this category that is inconsistent with the current pathway and the overall medicines framework. Further consideration is needed of the wording "pursuant to a risk-based approach, medicines with high level indications that require the intervention of a healthcare practitioner must be individually assessed for safety, quality and efficacy before being supplied in Australia." This definition aligns to an S3 or S4 classification, which is not consistent with the majority of registered complementary medicines, and thus it does not provide an appropriate reflection of the current risk level for registered complementary medicines. Although these products may pose a higher level of risk in relation to the indication or the scheduling of ingredients, these products do not all require intervention of a healthcare practitioner. A more appropriate definition for high level indications needs to be developed and provided for consultation prior to any legislative changes.

3.2 Do you envisage any difficulties with criteria used to include or exclude products from the new pathway?

As identified under question 3.1, ASMI notes significant concerns with the proposed criteria to include or exclude products from the new pathway. Consideration of the evidence criteria is required so that the category is fit for the proposed purpose. Current standards are prohibitive for some product types including those that are clinically robust, however further discussion will be provided in regards to the evidence framework.

Specific criteria needs to be created for addressing public interest criteria for restricted representations.

3.3 What other considerations may need to be taken into account in implementing the new pathway?

Consistency with the Principles of the Recommendation

Recommendation thirty-nine of the Expert Review, and the Government support for this recommendation, was for an additional assessment pathway to increase flexibility for sponsors and support innovation, as well as provide transparency for consumers. The current proposal is predominantly a partition of the existing listing system. The principles presented in this consultation paper very much indicate that a significant proportion of the products in the new pathway will be drawn from the ingredients and indications already utilised for listed medicines.

While the views have been expressed by the regulator that no products that are consistent with the risk criteria for the current listing pathway will be affected, there is a lack of transparency of which products the TGA believes are not consistent with the risk criteria as all available listed products have met the TGA validation rules to gain entry to the ARTG. Changes to the interpretation of the risk criteria will have a significant impact on current sponsors who will be forced to amend indications or adapt to a new risk category and its associated requirements. The TGA proposal does not appear to be consistent with the Government response, or the recommendation from the independent Expert Review, therefore it should be evaluated if these reforms require a regulatory impact statement.

Restricted representations

A clearer description of the public interest criteria for a restricted representation for each pathway is required. The consultation paper notes that "there are limited circumstances where it would be in the public interest for a low risk medicine (which had not been individually evaluated for efficacy) to refer to a restricted representation on the medicine label", further clarification of this statement is required to understand the intention. As identified previously, abandoning the public interest criteria for listed complementary medicines to carry approved restricted representations needs to be carefully considered. There needs to be a continuum within Government decisions so that there is consistency between low risk complementary medicines, the allowance of food fortification and health claims, along with other low risk, non-complementary therapeutic goods such as sunscreens.

ASMI does consider that there could be benefits for assessing most new indications referring to restricted representations through the new pathway or registration pathway if this assessment can also equate to an advertising exemption for the restricted representation. The TGA has not made it clear whether the proposal for restricted representations approvals will be managed simply as part of the product evaluation or whether this will continue to require a two stage approval process. It is also unclear to ASMI how approvals to use restricted representation will be addressed as part of the advertising reforms. There is little justification for maintaining a complex system that requires two separate assessments for the same indication, instead the current dual process is time consuming, inefficient, a duplication of regulatory function, and creates business uncertainty.

Further consideration should also be given to approved 'high level health claims' in foods that would equate to restricted representations for complementary medicines, and where sufficient evidence and a significant public health benefit is supported, a process should be available for enabling these indications for low risk, listed complementary medicines.

Biomarker Indications

Biomarker indications that are genuinely consistent with the definition of a listed medicine and are supported by appropriate evidence, should be able to remain as listed medicines and be reflected in the permitted indications list. Instances where evidence for biomarker indications have been subjected to post-market review and considered acceptable should not be expected to generate new evidence to transition into the new pathway. Where evidence is based on a higher risk population, while still being suitable for self-management, the available indications through the new pathway should be able to reflect the target population and refer to the actual impact on the identified biomarker. This capacity would encourage higher quality research into complementary medicines to assist in the management of some conditions.

Suitability of the Permitted Indications list

A comprehensive and functional permitted indications list is critical to the success of the reforms.

Specificity of Indications determining pathway

ASMI does not agree with more definitive or more specific indications automatically placing a product into the new pathway. The TGA example of intermediate indication of "improves symptoms of common cold such as sore throat and runny nose within two days" while being more specific it does not fit into the above category of potential adverse health consequences if medical advice or treatment is delayed. Therefore the classification of this indication as intermediate risk is not consistent with the proposed framework. This should be a low level indication (Improves symptoms of common cold such as sore throat and runny nose) plus a claim (within two days). A claim of how fast something works is not part of the indication for use, even for registered OTC medicines.

Terminology

The terminology of "treatment, prevention and alleviation of a disease ailment, defect or injury" to identify the risk of a product has been consistently problematic as there is no qualification of whether these terms are indicative or specific. Given that preventing means to stop something happening, and alleviating means to lessen or relieve, this conflicts with the examples provided that refer to the relief of symptoms. As addressed previously, greater clarity is required over the intended meaning of this statement, or an alternative description which is less ambiguous would also serve to improve the consistency and understanding of the regulatory framework.

Further to this, there are a broad range of existing indications using the descriptors of treatment, prevention, and alleviation that are suitable for listed medicines. These include a range of indications for sunscreens, as well as the following examples:

- For the prevention and treatment of head lice.
- DECAY For the prevention of tooth decay (toothpaste).
- For the prevention and treatment of dandruff.
- MUSC3 Assists in the prevention of muscular cramps and spasms.
- TINEA2 treatment of tinea by topical application.

Treatment, prevention and alleviation as actions in an indication themselves do not necessarily mean that a consumer may suffer adverse health consequences due to delaying seeking medical treatment or advice. Conversely, it could be argued that medicines for prevention or to reduce the risk are not going to delay someone seeking medical advice as these are usually in the context of a healthy population.

Non-permitted indications list

ASMI questions the necessity for a non-permitted indications list given mechanisms are already available, such as through the permitted indication list and the evidence guidelines that would already restrict the availability of an indication. ASMI questions whether this mechanism provides benefit in simplifying the regulatory system or if this adds a new level of complexity and maintenance.

Other potentially non-permitted indications, such as those identified in the consultation paper referring to vulnerable populations, are dependent on the context rather than the application of blanket restrictions. Instead of including vulnerable populations on a non-permitted indications list that excludes all indications, this should be controlled by indication or by ingredient as per the current practice of warning statements and restrictions.

Approaches to establishing efficacy
3.4 Do you agree with the proposed methods to establish efficacy for products included via the new pathway?

ASMI holds significant concerns regarding the application and accessibility of the proposed methods for establishing efficacy and does not support the current proposal. It is acknowledged in the consultation paper that the evidence for complementary medicine indications is largely based on published studies and sponsors rely on information in the public domain. The paper also acknowledges that most of this information is for individual ingredients rather than formulations/products. While some sponsors may generate their own studies this is very costly and not widespread, particularly for products which are not regulated as medicines in other jurisdictions and do not require this level of evidence. In order to have a medicine approved under the new pathway, sponsors will be required to establish efficacy based on the finished product rather than ingredients. This proposal therefore creates a new standard for efficacy data for many products that are currently considered appropriate for inclusion on the ARTG.

ASMI also holds concerns regarding the requirement for product specific evidence under the proposed method 1. The proposal indicates that in some instances sponsors will be required to generate clinical data and have this assessed through the new pathways, within the proposed transition period, in order to maintain the product on the market. It should also be noted that clinical trials are often extremely difficult to develop for many non-specific indications, as any long term preventive study is typically cohort based, requires many years of data to produce a number needed to treat to define incidence reduction, and are expensive and difficult to conduct on an individual, specific product for the necessary duration. The requirements for establishing efficacy need to reflect appropriate study methodology. Requirement for product specific evidence for

intermediate level indications, which are proposed to include restricted representations, would also mean well researched ingredients such as folic acid and vitamin D would be required to conduct product specific clinical trials, which is prohibitive in regards to ethics approval.

The proposed method 2 for establishing efficacy is also problematic, and all products that don't meet the criteria for method 2 appear to require clinical data on the actual product. Method 2 is only available for products where active ingredients are defined chemical entities such as vitamins, minerals and amino acids, and requires the provision of bioequivalence data. Firstly, it is not clear what product bioequivalence needs to be demonstrated in relation to, and if it is therefore a requirement for first-to-market products through the new pathway to hold clinical data. Secondly, there appears to be no provision for allowing justification for not providing bioequivalence and bioavailability data, as included in the EU Guidelines. Thirdly, herbal based products, animal products and probiotics are ineligible for using method 2 to establish efficacy, therefore a sponsor who wants to gain approval for a herbal tablet via the new pathway must perform a clinical trial on their product. The restriction of method 2 means that any future line extensions, changes to dosage form or reformulations will require a new clinical trial. The outcome of this is that the new pathway will likely only be used for a very limited number of products due to the cost of running the clinical trials.

Further to this, registered OTC products are able to establish efficacy and safety for new indications using literature-based submissions, which is a significantly lower barrier than this proposal for lower risk products. Therefore, the proposed methods for establishing efficacy are likely to be a huge disincentive to innovation for complementary medicines and are out of step with the medicines framework.

3.5 Is the proposed approach to establish efficacy for current listed products that have a restricted representation exemption appropriate?

ASMI does not support this proposed approach and does not agree that current listed products that have restricted representation exemptions should be required to transition to the new pathway. ASMI also does not agree that the proposed approaches to establishing efficacy adequately accommodate the range of indications and products that could fit into this category. As addressed previously, clinical data on the finished product is not suitable for conducting long term prevention studies, such as calcium and vitamin D for osteoporosis prevention, or for generating product specific data for higher risk conditions where there is already a substantial body of evidence, such as folic acid for neural tube defects.

While clinical data on the actual product is desirable and should be encouraged, alternative mechanisms need to be available where there are ethical or functional limitation to study design that may make this standard unreasonable to achieve. Therefore, there needs to be scope to accept high quality literature submissions, and justification for not providing bioequivalence data, instead of clinical data on the finished product for all product types including herbs and herbal extracts.

Evidence requirements
3.6 Are the evidence requirements appropriate for the new pathway?

Apparent requirements for first-to-market to hold clinical trial data is a significant barrier to entry, as many products will not be able to attain this evidence on the actual product for higher risk indications or indications where there is an established treatment protocol. An ingredient based justification along with a suitable dissolution profile, should be sufficient to provide evidence for the product.

Additionally, based on table 3 it would appear that traditional indications cannot be used, even as secondary indications for a product assessed through the new pathway. Clarity is required on this point, particularly in the context of herbal ingredient where much of the evidence base is traditional in nature. We note the consultation paper also states - "We propose that the following products will **not** be accepted for evaluation through the new pathway for: …Products that have indications based **solely** on evidence of traditional use, unless they also provide adequate scientific evidence supporting the indications." – which indicates traditional use would not be accepted as supporting evidence.

The proposed minimum literature requirements should also allow for an 'other' category, such that other evidence where justified could also be considered within the evidence pathways. This will provide a more flexible regulatory framework without compromising the rigour and credibility of the TGA. Additionally, evidence should be considered from overseas or other national regulatory agencies to support efficacy. Peripheral to recommendation forty-six and the focus on efficacy monographs, there is capacity for evaluation and submission processes to be streamlined.

3.7 Do the proposed levels of assessment align with the proposed risk-based hierarchy?

The proposed minimum levels of evidence for the revised framework do not align with the risk based classification of the products and ingredients within the framework. The levels of evidence requirements have ignored the active ingredient and whether it is novel or well characterised. The evidence levels have been set as a one size fits all whether the active is 'new' to the ARTG or a well-established vitamin.

There is a significant and concerning disconnect between the evidence requirements for complementary medicine products having intermediate and/or high level indications' and the requirements for OTC medicines. The safety and efficacy data requirements and criteria in regulatory guidelines for OTC medicines are clear:

a) It includes criteria when bioequivalence data are required to be provided in the application or justification for not providing one;
b) List of actives that do not require bioequivalence data when used in generic OTC oral medicines (Vitamins and Minerals have known safety profiles and could fall into this category)

There is no such clarity within the proposed criteria, with the requirements proposed in the reform for complementary medicines being far more restrictive than those for OTC medicines, where instead there should be alignment with the efficacy data requirements for products with comparable risk.

The consultation paper also describes registered complementary medicines as having 'high level indications referring to the prevention, alleviation, cure or management of a serious form of a disease, ailment, defect or injury.' However this is only one aspect, it ignores that unlike listed medicines, the ingredients are not limited to the permitted substances list and that they may contain new ingredients or those that are subject to a schedule of the poisons standard. While this does introduce an additional risk source to control, at the same time a scheduled ingredient may support a low level indication. Therefore, the contributing risk factors for complementary medicines change between listed to registered products, and this is not necessarily an easily conceptualised risk-continuum.

3.8 What other considerations may need to be taken into account in implementing the new pathway?

Further details of the process for application, review, response to questions, appropriately addressing possible safety concerns are all needed. Additionally, whether the combination of a higher risk indication or reference to a vulnerable population is likely to trigger a request for safety data which goes beyond the proposed scope of the new pathway. Timeframes for clarity, transparency and predictability of the process also need to be made available.

Inclusion of export only medicines and whether submission via the new pathway will be required for some products. This may have negative impacts on Australian business with supply channels looking to more accessible markets to enable supply. The background indicates that complementary medicines exported from Australia are included in scope.

The three year transition period should start once all mechanisms are in place and available to allow a smooth transition, and both the application and evaluation fees should be waived for the whole 36 months.

Implementing a list of permitted indications

Criteria for permitted indications
4.1 Are the proposed criteria for inclusion of an indication on the permitted indications list appropriate?

ASMI generally agrees that the criteria for inclusion of an indication on the permitted indications list is appropriate, however a clearer legal definition of a serious disease or condition is required to ensure consistency in interpretation. Alternatively, as suggested in part 3, it could be beneficial to remove uncertain wording regarding serious diseases or conditions and instead revise the definition for low risk indications, as this could also help ensure an appropriate standard is maintained. The use of 'serious disease' as referenced in the Therapeutic Goods Advertising Code is broad and subject to interpretation. This contributes to a lack of transparency and consistency with the regulations.

Additionally, the criteria for whether an indication is permitted should focus on whether there may be adverse health consequences for the patient through delaying medical advice or treatment for a condition, and this should be the fundamental criteria in determining whether an indication is suitable for the low level pathway. An indication should not be excluded from the permitted

indications list just because it is more specific indication, references a vulnerable population, or includes a reference to an exempted restricted representation.

A non-permitted indications list may be helpful to sponsors; however this should be presented as a guidance document instead of a mandated/legislative document. Considering that the non-permitted indication list is to help sponsors decide if they need to go through the new pathway, it would be more useful as a criteria check that can be adapted easily rather than legislated.

4.2 What other considerations should be taken into account in implementing the permitted indications list?

See 4.4

Implementation of the permitted indications list
4.3 Is Option 2 for selecting indications for inclusion on the ARTG and on product labels and promotional material suitable to address the objectives for permitted indications?

ASMI supports the adoption of option 2, assuming that this list is developed through ongoing consultation with industry and seeks to provide a comprehensive and functional list. The consultation does state that the TGA would develop a comprehensive list of traditional and scientific 'core' indications and specify qualifiers for further consultation with stakeholders, and ASMI is supportive of this approach. Assessment of new permitted indications should not require or provide a surrogate evidence assessment, and approval should be based only on whether it meets the acceptance criteria for listed medicines. Further to this, Sponsors should have an opportunity to add a new 'core' or 'qualifier' to the list that would be available electronically.

4.4 What other considerations should be taken into account in implementing the permitted indications list?

ASMI holds concerns that the TGA has not adequately explained why listed indications that have been used for years and accepted by the TGA should change. These reforms have been presented as a deregulation initiative, however the current proposals are introducing new evidence requirements and restricting products and indications that meet the current regulatory framework.

There needs to be a very clear legal definition of what constitutes a low level and medium level indication. When applying for a new permitted indication sponsors need to have some precise definition so they can know that it is likely to be approved. This is also vital to the creation of the permitted indications list, so that justification against precise criteria is available as to why an indication should not be on the permitted indications list. It is also important that a mechanism to appeal a rejected permitted indication application is made available.

Claiming evidence of efficacy

Criteria for the use of a claimer
5.1 Do the proposed criteria for the use of a claimer address the objectives for the recommendation?

ASMI does not agree with this recommendation and does not believe that it is feasible to convey the complexity of information required in a sufficiently succinct form so as to practically fit into the space available. Therefore, it is unlikely that the proposed use of the claimer will be able to address the objective of the recommendation without being misleading and counterproductive for medicines generally.

5.2 What other considerations should be taken into account in implementing this recommendation?

ASMI does not support the introduction of a claimer for products assessed through the new pathway or for registered complementary medicines. ASMI considers the potential value of this recommendation for communicating the assessment status of a particular product is outweighed by the negative impacts this will have in creating confusion regarding other medicine types. Sponsors who have products that span complementary and OTC medicines are particularly concerned as providing the claimer on some products while not on others creates confusion of the efficacy and undermines the value of the brand. ASMI also holds concerns that this claimer implies that all listed medicines are not effective, and this is not consistent with the declarations that sponsors make in listing their products.

ASMI believes that implementing an efficacy claimer and/or symbol is misleading for Australian consumers. Consumers are not aware of how products are regulated in Australia, and it is difficult to envisage a succinct consumer-facing statement that is able to meaningfully convey the distinctions between three levels of regulation for complementary medicines, within the broader medicines context. Any statement is likely to contribute to misdirected expectations or doubt regarding the efficacy of products that do not have the efficacy claim or symbol.

ASMI instead suggests the TGA focuses on initiatives to improve consumer understanding of the regulatory framework through a well-constructed consumer education campaign. This should be subject to ongoing evaluation and development to ensure it is effective and evidence-based.

Use of a claimer
5.3 Will the use of a claimer on complementary medicines have any unintended consequences?

ASMI holds serious concerns that the introduction of an efficacy claimer to some classes of medicines is likely to lead to the following undesirable outcomes:

- A claimer is likely to be taken as TGA endorsement for a product.
- Consumers seeing a claimer on a product may choose that product in preference to a Registered OTC when the OTC medicine may be more suitable for them.

- Due to limited space on labels not all products that can use a claimer will be able to. Therefore when seeing a product that makes a claim and does not have the claimer it will not be readily apparent to consumers or competitors if the product is using the indication illegally or if it has been assessed by TGA but does not have the claimer on pack.
- For products that use the same label in other markets (e.g. New Zealand) the claimer on the label may not be acceptable in the other market.
- It creates an unlevel playing field between complementary, OTC and prescription medicines.
- Likely to create confusion amongst consumers, and health care practitioners.
- Consumers may doubt the efficacy of products that do not have the efficacy claim or symbol, such as toothpaste, sunscreen etc.

ASMI also have concerns how changes to the balance of evidence over time may impact the approval by the regulator and the assessment of efficacy. Clarity is required as to how a review of an existing evaluated product may be initiated and the expectations on the sponsor.

Presentation of claimers
5.4 Should the claimer be presented as a visual identifier as well as a statement?

The TGA should clarify if a distinct identifier is intended for the new pathway, similar to an AUST L or AUST R. Aside from a distinct identifier, ASMI does not support the use of any addition variety of claimer or symbol for efficacy.

5.5 Do you have any views on the possible wording or design of the label claimer?

The new pathway should be identified through a unique identifier, distinct to the current AUST L/R, otherwise this will contribute to further confusion. Consumer education focussed on understanding the differences between each of these categories is more beneficial, rather than trying to introduce a new claimer system that doesn't give the consumer a clear understanding of how a particular product relates to another medicine.

If a design is to be entertained for the claimer it should:

- Not introduce specific colour requirements as a unique colour to a label design will add to the cost of label printing and will not provide a pleasing aesthetic on all label design.
- Be consistent with the 1mm text height of AUST L number on the label – Be mindful of the already limited label space.

5.6 What other considerations should be taken into account in implementing the claimer?

If this proposal goes ahead, a review should be built into the implementation of the claimer to see if the overall impact is positive, negative or neutral. A review after 12-18 months with all stakeholders is not unreasonable, as well as a detailed investigation of the impacts on consumer perceptions. Ongoing evaluation of the efficacy of consumer facing education also needs to be incorporated into the impact assessment regarding the value of the proposed new pathway and consumer understanding of the medicines framework.

Incentives for Innovation

Protection for new ingredients
6.1 Is the proposed process and mechanism to provide market protection for new ingredient applicants appropriate?

ASMI has always supported incentives to encourage innovation. The proposed process and mechanism for providing incentives to new substances (to be included on the permitted substances list) lacks detail regarding how this will actually be applied. ASMI would support an applicant authorisation system where a product would not be able to be entered on the ARTG through the listing system unless the sponsor holds an authorisation.

6.2 Is the proposed 2 year period of exclusivity an appropriate period to reward the innovation and allow for a return on the investment made?

Two years is unlikely to be sufficient to compensate for the investment of applying for a new ingredient, and therefore may only have minimal benefit as an incentive to industry. Allowing sponsors sufficient time to list and produce a new product, including considering production and delivery lead times, as well as delays due to range reviews of retailers.

ASMI proposes a three year market exclusivity period for the original ingredient applicant.

6.3 Should multiple applicants be able to apply for exclusive use of the same new ingredients using their own data during the exclusivity period?

In principle ASMI agree with this recommendation, as prohibiting applicants from submitting their own data is likely to serve as a disincentive to innovation and research. This is of particular concern in the complementary medicines realm as the interest in an ingredient may be developed out of published efficacy research that supports the viability of the ingredient for the market. This has the potential that more than one applicant could be working on developing a substance application for a like substance, and therefore multiple applicants should have capacity to seek a return on their investment if they are using their own generated data. Unlike pharmaceutical ingredients, complementary medicines have a limited pool of substances on which to draw, so therefore consideration about the definition of innovation and how secondary applicants are treated needs to be considered outside the standard pharmaceutical intellectual property paradigm.

6.4 What other considerations should be taken into account in implementing the proposed incentive for innovation?

Review of the data requirements for new ingredient approval was not adequately closed out as part of the complementary medicines business process reform project and should be reviewed again as part of the implementation here.

Consideration of how details are communicated of new substances that are being held under an exclusivity period needs to be provided, such as approval and end dates, as well as when compositional guidelines for unique substances are made publicly available.

Protection for efficacy data
6.5 Is the proposed process and mechanism to provide data protection for efficacy data appropriate?

ASMI has always supported incentives to encourage innovation. There is a lack of clarity regarding the proposed process and mechanism, and therefore how data protection is going to be achieved is also not apparent. That said, in principle ASMI is supportive of the further review and development of this proposal.

6.6 Is the proposed 3 year data protection period for efficacy data appropriate to reward innovation and allow for a return on the investment made? Is it excessive?

ASMI would like to see more detailed financial and market modelling to determine what the optimum period of data protection is likely to be, however between three years and five years seems to be most desirable.

6.7 Should protection be available for new uses of existing substances and /or be available for information that is not in the public domain?

Sponsors that have their own data/clinical study should be able to use an indication even if another sponsor has made a submission for the same indication/ingredient. Protection should also be available if a sponsor conducts a clinical trial for a product for a new indication/use of an existing active ingredient, assuming that the protection only extends to the indication and not the substance in general.

Incentives to innovation should ideally contribute to the knowledge base and evidence should be open to critique/peer-review. Data protection is intended to provide a more reliable mechanism for ensuring a return on investment, without the data needing to be withheld. That said, it is not pragmatic for market protection to require information to be in the public domain prior to the market protection being granted. Further, requiring the data to be made available in the public domain once exclusivity has been granted is not always within the scope of control of the applicant. Journal editorial committees can hold papers for extended durations, which is out of control of the applicant, alternatively pay-for-publish journals do not have the same high reputation for peer-review, which could damage the perception of the data.

This raises a conflict between the intent and the practicality of the mechanism. Data protection should be granted on the merits of the data regardless of whether it is in the public domain, however sponsors should be encouraged to contribute to the available knowledge base.

6.8 What other considerations should be taken into account in implementing the proposed incentives for innovation?

Enforcement of data protection mechanisms have not been sufficiently identified. It would be useful to have confirmation on whether the TGA would refuse applications through the new pathway or registration pathway that is using protected data. Additionally, confirmation that if a sponsor who believes that a listed medicine is infringing on their data protection through self-certified 'imitation' indications is able to prompt the TGA to initiate a product specific post-market review, would also provide confidence in the proposed mechanism for incentives. Outside of this, it would appear that any other data protection action would be required to follow legal channels.

Implementation

Transition arrangements
7.1 Do you agree with the proposed principles to support transition arrangements?

In principle ASMI agree with duration of the transition period, however this should only commence when all mechanism are in place. Commencing a three year transition phase when the new pathway will not be available for the first year drastically impacts on the ability of sponsors to smoothly transition.

Transitioning to the new permitted indications framework, along with the removal of the free text box, without having all application pathways available is not going to contribute to an effective transition. Further to this, for products requiring new clinical trials to meet the evidence requirements for the new pathway, three years is unlikely to be sufficient to complete and publish clinical trial data to meet these requirements.

The cost structure of the transition also needs to be considered, as many products will be forced to make changes to the ARTG, including the addition of new coded indications, if fees are attached to all of these applications this is going to be a significant cost burden.

Finally, the feasibility of the new pathway will be dependent on the final evidence requirements, timeframes for assessments and the associated cost. Further detail, and consultation where appropriate, on the expectations for each of these matters is requested.

7.2 What other factors should we consider?

Impacts of other consultation papers, such as advertising and low risk medicines, are not clear. Further considerations may be identified as the content and intentions of these consultations become apparent.

Clarity is requested regarding the application processes for the transition and how the TGA with resource the additional work. Funds have been allocated for the development of the framework, however the ongoing funding arrangements have not been clarified.