

Response to the Consultation:
Reforms to the regulatory
framework for complementary
medicines
February 2017

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About Sanofi Consumer Healthcare

Sanofi Consumer Healthcare Australia is part of Sanofi, a global life sciences company committed to improving access to healthcare and supporting the people they serve throughout the continuum of care. Sanofi's global portfolio includes diabetes and cardiovascular, vaccines, rare diseases, oncology and consumer healthcare businesses.

In Australia, Sanofi Consumer Healthcare is one of the country's largest vitamin, mineral and supplement manufacturers and distributors. We are also a large supplier of trusted over the counter medicine brands.

With a brand portfolio that includes Nature's Own, Cenovis, Ostelin, Betadine, Gastrolyte and Telfast, our products are found in more than 8500 pharmacies and grocery outlets nationwide.

Sanofi Consumer Healthcare is based in Brisbane's northern suburbs, where our \$80 million, 35,000 square, TGA licensed and GMP standard vitamin, mineral and supplement manufacturing facility is located. Sanofi Consumer Healthcare is the only large-scale vitamin, mineral and supplement business in Australia to be vertically integrated with full research, development, manufacturing and packing capability. In recent years, we have invested in excess of \$30 million in this site to grow our Australian manufacturing presence. This investment ensures we remain at the forefront of high quality research, development and manufacturing.

We employ approximately 400 people across Australia including scientists, allied health professionals, regulatory affairs specialists, quality control experts, manufacturing technicians, engineers and warehouse staff.

Overview

Sanofi Consumer Healthcare (Sanofi) welcomes the opportunity to provide feedback on the Department of Health's Therapeutic Goods Administration (TGA) reforms to the regulatory framework for complementary medicines consultation paper, dated February 2017.

Sanofi agrees in principle that:

- removal of free text fields and implementation of a permitted indications list together with strengthened post market monitoring will improve compliance for complementary medicines
- an additional intermediate pathway for listing of a complementary medicine will provide an option for those Sponsors wishing to submit evidence for pre-evaluation to support higher level claims
- sponsors who have had the efficacy of their products assessed by the TGA should be able to include an appropriate 'claimer' on their labels and promotional material
- provision of market exclusivity for new ingredients will encourage further research in the sector
- introduction of data protection for those Sponsors who have invested in clinical research for their products to support higher level claims will support innovation in the sector
- a transition period of 3 years post implementation of all reforms to the regulatory framework i.e. new pathway, permitted indications list and evidence guidance is appropriate

However, Sanofi does not agree that the options presented in the consultation paper relating to the criteria for the low and intermediate level indications and evidence requirements for the new pathway are appropriately aligned with the regulation of low risk products. A number of proposals will increase the regulatory burden for sponsors with no benefit to public health and safety. Thus they will not deliver on the original intent of the medicines review, namely to identify ways to improve access to therapeutic goods for consumers and remove unnecessary red-tape for industry, whilst maintaining the safety of therapeutic goods in Australia.

Criteria for Low and Intermediate Level Indications:

Sanofi considers that the use of appropriate qualifiers for structuring a permitted indication provides an acceptable method to represent the evidence that refers to non-serious diseases/ conditions or well-known biomarkers to enable consumers to make an appropriate product selection for their needs. Existing indications on the TGA database (including those recently approved via post market reviews of evidence) should therefore be retained for use as low level indications. In the absence of further details on the proposed permitted indications list the impacts of potential changes described in the current consultation on Sponsors cannot be fully assessed.

The current consultation paper does not address recommendation 46 which relates to efficacy monographs for commonly used active ingredients that have been approved for use in listed medicines. These would document the evidence for specific indications and other relevant

information, reduce the burden for industry and ensure accurate information is available for consumers.

This approach parallels that used in the regulation of well-established over the counter (OTC) medicine ingredients such as aspirin, ibuprofen and paracetamol. For these ingredients a list of representative indications is provided in Appendix 5 of the Australian Regulatory Guidelines of Over the Counter Medicines (ARGOM) which Sponsors can use without any requirement for supporting efficacy data. Considering OTC medicines are associated with significantly higher risks than the permitted ingredients included in complementary medicines, the level of regulation should reflect the risk hierarchy and monographs are a key consideration in developing any evidence criteria under the new framework. In the absence of monographs the data requirements to support indications for well-established ingredients used in listed complementary medicine will be significantly higher than for well-established ingredients used in registered OTC medicines.

It is Sanofi's view that examples of commonly used ingredients that would fulfil the monograph criteria are those for which the TGA has issued restricted representation category permissions in the public health interest (folic acid for helping to prevent neural tube defect and Vitamin D and calcium for helping in the prevention of osteoporosis). Listed medicines containing these ingredients have been used for many years and evidence for their use has been well-established.

Under the consultation proposals, restricted representations are no longer allowable as low level indications for listed medicines and automatically require use of the new pathway and associated evidence requirements. Sanofi does not agree that this is appropriate for well-established ingredients as outlined above. Therefore, the transition plan cannot be executed as described in the consultation paper without significantly increasing regulatory burden, counter to the intent of the medicines review.

Alternative approaches that need to be subject to further consultation with industry include the following:

- a) allow exemptions from the new pathway for existing restricted representations so they remain as acceptable low level indications
- b) waive the evidence requirements for existing restricted representations considering these have already been evaluated by the TGA
- c) create monographs that capture the restricted representations for common ingredients that replace the need for Sponsors to provide efficacy evidence under the new pathway

Evidence Requirements for the New Pathway

The proposed options to provide evidence of efficacy for the new pathway exclude a full literature based approach that is an option for both prescription and OTC medicines. Generating bioequivalence and comparative dissolution data may not be viable in all cases, particularly when an original 'reference product' is no longer available on the market, considering the fast moving consumer goods environment that is very different compared to the markets for OTC and prescription medicines. Evidence based on an appropriate scientific justification by the Sponsor should thus be available as part of a third literature based option for generating evidence.

Summary

In summary Sanofi agrees in principle with a framework for complementary medicines that provides Sponsors with a choice of pathways reflecting a hierarchy of evidence. However, the following aspects of the proposed reforms need to be addressed to ensure an appropriate risk based approach is implemented considering the lower risk profile of complementary medicines:

- Clarification on the use of qualifiers to enable existing listed complementary medicine indications to remain as low level indications
- Further details on the proposed permitted indications list and plans for development/ adoption of monographs for common ingredients
- Maintenance of existing restricted representations for use as low level indications or waiver of evidence requirements as part of the transition plan
- Options for an additional literature only based approach based on both evidence for ingredients and finished product to support the evidence package for intermediate indications where bioequivalence or comparative dissolution data are not a viable option.

Sanofi Consumer Healthcare has taken the opportunity to answer the specific questions posed in the consultation where there is sufficient detail to evaluate the impact upon industry sponsor and to highlight areas that need to be reconsidered in more detail before further development. Sanofi welcomes the opportunity to further engage and collaborate with the TGA to create an optimum framework that delivers the appropriate level of protection for consumers and reduces regulatory burden for Sponsors.

Risk-based hierarchy for therapeutic indications

- 3.1 Do you agree with proposed indications hierarchy and the criteria proposed to distinguish the three medicine pathways?
- 3.2 Do you envisage any difficulties with criteria used to include or exclude products from the new pathway?
- 3.3 What other considerations may need to be taken into account in implementing the new pathway

3.1

Sanofi Consumer supports the principle of the new assessment pathway to provide sponsors with incentive to conduct further research into complementary medicines and provide a pre-evaluated pathway for listed complementary medicines with higher level indications.

However, Sanofi Consumer Healthcare recommends the proposed indication hierarchy be reconsidered to take into account the existing regulatory framework and explore all opportunities to balance the existing and proposed framework, the reasons include:

- The proposed indication hierarchy will restrict the available indications for the self certification pathway and remove indications already evaluated and agreed by TGA delegates to have satisfied the public interest criteria via restricted representation approvals and post market review of selected products evidence packages.
- A new pathway for evaluation of higher level indications should be an option to sponsors who wish to generate additional clinical data. It should not be mandatory to require existing products with previously agreed indications via recent post-market reviews or restricted representation approvals to have to re-apply and generate additional clinical or bioequivalence data to maintain the existing product.

Sanofi Consumer Healthcare proposes that the indication hierarchy should be changed to include all existing listed indications already available within TGA's indication database on eBS in the low level self-certification classification, particularly those approved via recent TGA post-market review and restricted representation advertising exemption approvals. These recently approved indication and evidence packages have recently had a TGA evaluator review the evidence. Therefore, the current agreed indications should be suitable for a listed medicine indication classification and suitable for a listed medicine to advertise a specific restricted representation

3.2

Sanofi Consumer Healthcare envisages some difficulties with the criteria used to include or exclude products from the new pathway, including:

- Existing listed complementary medicine products with well-established ingredients and indications within the Australian market will be required to generate bioequivalence or comparative dissolution data. Additional data generated on well-established ingredients and known indications is not likely to contribute significantly to the research base of complementary medicines, however it will create another layer of regulatory burden with significant resource and cost implications for these well-established ingredients. As a consequence the evidence requirements will be higher than required for well-established ingredients including in registered OTC medicines, such as aspirin, paracetamol and ibuprofen, where sponsors are not required to supply any efficacy data. This does not align with the intent of the medicines review.
- The expert panel review recommended additional pathway for “higher level” listed indications and Sanofi Consumer Healthcare does not believe this was intended to encompass reclassification of existing listable indications. It is recommended to explore all opportunities to include the existing listable indications into the low level self-certification pathway and permitted indications list. This should include actions aligned with recommendation 46 to establish monographs which would exempt Sponsors from generating bioequivalence or comparative dissolution data for well-established ingredients and indications.
- Herbal products are stated in the TGA consultation document as being unable to utilise method 2 of the proposed new pathway. This should be re-evaluated to consider herbal extracts with a standardised component where that component has been demonstrated to be the active component of the ingredient.
- Low level indications which include a reference to a “a disease, ailment, defect or injury other than a serious form of those diseases” requires clarity as the practical application of this proposal will depend on the interpretation of this definition. The interpretation of “non-serious form” has in the past been quite variable and can depend on the knowledge or experience of the evaluator or sponsor and such terms may also be interpreted differently by healthcare professionals and consumers. A clear list of non-serious forms of diseases or conditions will need to be generated as a guide for sponsors to prevent inadvertent non-compliance with this definition.

3.3

Other considerations that may need to be taken into account in implementing the new pathway include:

- Guidance required for sponsors when there is no existing pre-evaluated product for comparative dissolution data profiling, which will be the case for a range of existing listed medicines.

- Additional consultation with stakeholders will be required for associated guidelines to develop new evidence requirements associated with the three proposed pathways. This guideline development is recommended to be developed in detail with stakeholders prior to further consideration of the intermediate indication new pathway. This will enable more meaningful feedback from stakeholders on the impact of the changes, and assist in the application of the new pathway.
- The overall cost and timeframe to have a product evaluated via the new pathway is not provided at this stage by TGA. Therefore, this does not enable industry to evaluate the feasibility for this option and makes it difficult to provide meaningful feedback on the impact to businesses. The regulatory cost impacts need to be considered prior to implementation of the new pathway.

Approaches to establishing efficacy

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

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

3.4

Sanofi Consumer Healthcare considers the proposed methods to establish efficacy for products included via the new pathway to be generally suitable only if selection of this pathway is by choice of the sponsor. However, we do not support the requirement for a bioequivalence data efficacy package for products forced into this category with existing approved listed indications.

3.5

The proposed methods to establish efficacy for products proposed by the reclassification of existing listed indications that have a restricted representation exemption is not appropriate. In this case, some restricted representations that have already been deemed by the TGA to meet the public health interest criteria, would require generation of additional evidence, which may be cost prohibitive for many sponsors, when existing information already supports the indications.

Three ingredients (folic acid, calcium and vitamin D), currently have industry wide advertising exemptions to use of restricted representations for certain serious diseases. These ingredients have clearly satisfied the criteria for providing a public health benefit, as they have already been evaluated by the TGA and the associated indications are permitted for use in advertising with certain conditions. Therefore, this should continue to be allowed by an exemption to include the associated indications in the permitted indications list for use in the low level self-certification pathway with additional listing conditions for

performance of dissolution testing. This is currently required for folic acid to comply with the BP monograph testing and would not increase the regulatory burden to continue this requirement. A similar requirement for calcium and vitamin D for disintegration testing or quality of active ingredient in the daily dose could be added as a listing condition for use of these restricted representations. This would reduce the need for sponsors to provide comparative dissolution data for each product with these well-established ingredients via the intermediate pathway. As previously referenced the establishment of monographs, as anticipated in recommendation 46, could be used to address these concerns.

Additionally, for new higher level indications, clarity is needed on alternatives for bioequivalence or comparative dissolution for products to fit within the intermediate level if there is no comparator product that has been pre-evaluated.

Evidence Requirements

- 3.6 Are the evidence requirements appropriate for the new pathway?
- 3.7 Do the proposed levels of assessment align with the proposed risk-based hierarchy?
- 3.8 What other considerations may need to be taken into account in implementing the new pathway?

3.6

The proposed methods to establish efficacy for products proposed by the reclassification of existing listed indications into the new pathway are cost prohibitive for many sponsors and not appropriate for the indications proposed to be reclassified into the new pathway. As previously expressed, forcing restricted representations into this pathway for some well-established ingredients and indications (folic acid, calcium and vitamin D) places restrictions on the industry for well-known ingredients with a low safety risk that are already established as being in the public health interest to provide indications relating to neural tube defects or reducing the risk of osteoporosis.

An additional option for full literature review evidence package needs to be included as appropriate for the new pathway, without the requirement for bioequivalence or comparative dissolution data.

Clarity is needed on the bioequivalence or comparative dissolution for products to fit within the intermediate level if there is no comparator especially for existing products which will fit within this new pathway.

3.7

The proposed levels of assessment do not align with the proposed risk-based hierarchy, particularly for listed medicines that may be forced to use the new pathway.

There should be an option for a full literature review submission for listed medicines via the new pathway, without a requirement for bioequivalence or comparative dissolution data. The reference provided in the consultation documents is for biopharmaceutical studies for prescription medicines and is not the appropriate level to apply to low risk ingredient products particularly when these products will not have market exclusivity options available for products that contain well-known ingredients and indications.

As restricted representation advertising exemptions have already been approved based on literature review support for existing listed medicines, deliberately raising the bar to included bioequivalence data is not justified. This represents over-regulation, especially when considering the OTC medicines framework that requires no efficacy data to support a range of indications for well-established ingredients including aspirin, paracetamol and ibuprofen that have a significantly higher risk profile than permitted ingredients in complementary medicines.

3.8 Additional considerations include

- Assess all options for exemptions from data generation requirements, including establishment of monographs as intended based on recommendation 46 of the medicines review panel report.
- Reviewing the cost implications of additional regulatory burden of clinical or bioequivalence data requirements for products if these criteria remain for the intermediate new listing pathway.
- Determination of the impact where comparative dissolution data is not able to be provided due to a lack of pre-evaluated originator product, and the cost implications for industry for well-established ingredients.
- If the evidence package for an intermediate indication can be supported based on the ingredients alone, then there is a question as to why there is a need for comparative dissolution or bioequivalence especially if there is no similar product currently on market.
- Clarity on the clinical trial requirements to satisfy expectations for the new pathway option 1. This would assist sponsors to ensure trials are conducted of the appropriate size and power to ensure outcomes are suitable to support intermediate listed indications. We suggest clear examples of the standard of trials needed could be included in guidance documents or an option for pre-submission approval of the trials by TGA.

Criteria for permitted indications

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

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

4.1

Sanofi Consumer Healthcare agrees with the general principles for an indication on the permitted indications list, however these indications need to include all currently listed medicine indications.

Sanofi Consumer Healthcare proposes that the permitted indications list criteria should be changed to include all existing listed indications already available within TGA's indication database on eBS in the low level self-certification classification. This should also include those approved via recent TGA post-market review and restricted representation advertising exemptions. These have had a TGA evaluator review the evidence recently and agree the indications are suitable for a listed medicine classification.

4.2 Other considerations to be taken into account for the permitted indications list include

- The inclusion of all existing listed indications in the permitted indications list.
- The inclusion of existing listed indications recently approved in restricted representation exemptions.
- The inclusion of existing listed indications recently approved via post market review by TGA evaluators.
- Consideration of how to include suitable target for permitted indications list to cover the unique expressions used in many traditional medicine texts. Sufficient guidance on how traditional terms will be translated may need to be discussed in stakeholder workshops to ensure the available list covers the various traditional paradigms.
- The terms needed to cover traditional paradigm targets may not be available at the time of creation of the permitted indications list until each traditional texts or product is evaluated. As this will be completed by most sponsors during the fee exemption period, requiring sponsors to pay for each additional indication target creates a financial burden on sponsors. Sanofi Consumer Healthcare suggests that adding additional targets or qualifiers during the first few years of the permitted indications list should be considered to prevent unnecessary additional regulatory costs.
- Further clarity on restricted representations and the avoidance of implying a serious form of a condition by use of qualifiers is needed. Many existing products may only need a minor adjustment to include qualifiers such as "mild" or "minor" to be included in the low level indications. This clarity is needed by sponsors before

assessing the implications of the new pathway and implementation of the permitted indication list.

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

4.3 Sanofi Consumer Healthcare agrees that Option 2 is the preferred option for implementation of the permitted indication list. This option will be less time consuming in ensuring all current listed indications are covered, and will still allow for differentiation between sponsors

4.4 Other considerations include:

- Ensuring there are clear guidelines on the variation of rewording of the permitted indication for label and promotional material
- Examples expressed in the consultation document need to be expanded and developed further during stakeholder workshops to assist sponsors with the assessment of existing potential product indications and which of the proposed listing pathways would be applicable.
- Ensuring clarity on how permitted indications may or may not be reworded for labels and promotional material. This would assist inadvertent non-compliance due to rewording a permitted indication inappropriately.
- Ensuring clarity with guidance on use of the permitted indications list option within eBS of how to use qualifiers to prevent an inadvertent non-compliance with a potential serious form of a condition.

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

5.1 Sanofi Consumer Healthcare agrees with the principles of the proposed criteria for use of a claimer on pre-evaluated complementary medicines.

5.2 Other considerations to be taken into account include:

- Any additional resource requirements for monitoring required by the TGA use of the claimer on product label and promotional material.
- The potential for additional cost to sponsors and impact on TGA resources for evaluation of variations in approved promotional material and labels for products assessed via the new pathway and registered pathway.

Use of a claimer

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

5.3

An unintended consequence of a claimer on complementary medicines may include the potential for these products to appear a higher standard than registered OTC medicines to consumers. Registered OTC medicines are pre-evaluated for safety, quality and efficacy but cannot include a claimer on product label or promotional material.

Presentation of claimers

5.4 Should the claimer be presented as a visual identifier as well as a statement?
 5.5 Do you have any views on the possible wording or design of the label claimer?
 5.6 What other considerations should be taken into account in implementing the claimer?

5.4

Sanofi Consumer Healthcare believes the use of a symbol will require additional and ongoing consumer education to ensure the symbol is understood, as there is frequently limited space on labels/packaging, a written claimer should suffice.

5.5

Sanofi Consumer Healthcare prefers a short claimer due to limited space on product packaging and reference to the TGA in the wording of the claimer. The term “independently assessed’ is unlikely to be seen as high value and not clearly understood by consumers as it does not explain who has assessed the product. The example claimers that reference the TGA would be suitable, with the last statement preferred “Evidence has been reviewed by the TGA”. Use of the term “TGA” is considered to be needed within the claimer statement to incentivise industry to invest money into research.

5.6

Other considerations that should be taken into account in implementing the claimer are:

- Need for clear guidance on placement on packaging and promotional material

- Need for education of healthcare professionals and consumers of the meaning of the claimer and the associated cost of an education program.

Protection for new ingredients

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

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?

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?

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

6.1 Sanofi Consumer Healthcare agrees in principle with the proposal regarding the process and mechanism for protection of new ingredients.

6.2 Sanofi Consumer Healthcare agrees in principle with the proposal regarding the period of exclusivity.

6.3 Sanofi Consumer Healthcare agrees in principle with the option for multiple applicants, if the sponsors have generated their data independently.

6.4 Other considerations for this proposal on market exclusivity must only be applicable to new ingredients to the Australian permitted ingredients. It cannot be applied to combinations of existing permitted ingredients for listed medicines.

Protection for efficacy data

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

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?

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?

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

6.5 Sanofi Consumer Healthcare agrees in principle with the proposal process and mechanism on data protection for efficacy data.

6.6 Sanofi Consumer Healthcare agrees with the proposal for a period of data protection for efficacy data package and believes 3 years is suitable for the level of investment

6.7 Sanofi Consumer Healthcare considers that protection could be made available for genuinely new uses of existing substances, however it should be a requirement to demonstrate the use is not in the public domain for that substance, including use of the substance in international markets.

6.8 Additional considerations include:

Data protection for products using a clinical trial with reference to a specific brand named product or specific formulation could be made an available option, however this should not be implemented in such a manner as to prevent other sponsors generating their data on a similar product and indications independently. If a sponsor wishes to conduct clinical research on existing combination products, the sponsor should be able to apply for pre-evaluation via the new pathway and utilise the positive “claimer” on label and promotional material.

Transition arrangements

7.1 Do you agree with the proposed principles to support transition arrangements?
7.2 What other factors should we consider?

7.1

Sanofi Consumer Healthcare does not support the proposed principles for transition arrangements with regard to the exemption from fees. Sanofi Consumer Healthcare does agree that a total 3 year transitions is likely to be sufficient.

As there will be a large financial and personnel resource burden on sponsors to revisit the new evidence and listing requirements and for those sponsors with large portfolios, the 18 months exemption on fees is not sufficient. For example, Sanofi Consumer Healthcare has over 400 ARTG entries in listed complementary medicines and in our past experience when ELF 3.0 was introduced, the complete review of each existing product will take well over 18 months. Once the details of the new permitted indications and evidence requirements for each pathway is known in more detail, a more detailed estimate of the timeframe needed could be provided by sponsors.

7.2

Other factors to be considered include:

- This proposal is a major change to the Electronic Business Services application requirements for listed medicines. There needs to be sufficient TGA resources and testing of the new application database prior to implementation.