Reforms to the regulatory framework for complementary medicines

Consultation Paper

Response – 27th March 2017

Nestle Australia Ltd appreciate the opportunity to respond to the consultation paper on reforms to the regulatory framework for complementary medicines.

Nestlé Australia Ltd produces a small range of products that are regulated as medicines. These products include listed medicated throat lozenges under the brands SOOTHERS, BUTTER-MENTHOL, ANTICOL and THROATIES and listed and registered chewable antacid products under the brand QUICK-EZE. These are iconic Australian products that have been are manufactured in Australia for over 50 years and are supplied to the Australian and New Zealand markets.

- Nestlé supports the recommendation that a new intermediate assessment pathway be made available for listed medicines. This is provided that, as described in the objectives of the reform, all listed medicines on the ARTG with indications currently appropriate for listed medicines will be able to select equivalent indications from the permitted indications list.

  The objective of the reforms describe the new pathway as allowing higher level indications than are currently able to be accessed by listed medicines. Consistent with this objective, no listed product currently on the ARTG with suitable indications should be required to transition to the new pathway in order to maintain those indications.

- Nestlé do not support the proposed evidence requirements of the new pathway as they are not suitable for complementary medicines and inconsistent with the level or risk of the products.
- Nestlé do not support the introduction of a claimer for complementary medicines as this is likely to be seen as TGA endorsement of the product, may cause confusion for consumers who see this endorsement on some complementary medicine labels but not on OTC medicine labels or other complementary medicine labels.

- Nestlé support the introduction of market exclusivity for applicants for new ingredients for use in listed medicines and where sponsors have conducted clinical trials on their own product formulation in order to establish efficacy.

Our detailed response to the consultation is included below.

Risk Based approach for Therapeutic indications

3.1 – 3.3

The proposed intermediate pathway has been described as a pathway that is above that which is appropriate for listed medicines currently. The purpose outlined for this was to provide additional flexibility for sponsors to access higher level indications than are currently permitted for listed medicines.

Nestlé support the intent of the reform provided that all products that are currently listed on the ARTG with appropriate indications would be able to maintain those indications via the permitted indications list pathway. Consultation on the permitted indications list will need to be undertaken to ensure all required indications are identified and included on the list.

Nestlé has concerns about the risk based hierarchy described to define the intermediate level indications. The distinction, based on risk, needs to be clearly and unambiguously defined so that it can be easily agreed which classification an indication belongs in and that it is not subjective and open to opinion.

With the implementation of the new pathway it appears that this reform could be used to push some products that currently have indications for use appropriate for listed medicines to the new pathway. This would be effectively introducing new requirements for these products and goes beyond providing additional flexibility and access to higher level indications to increasing the requirements for some products.

Further consideration is required to define the criteria of the proposed new category so that it is above the current listed pathway.

The risk factors considered on page 7 and 11 the consultation document in determining the classification of an indication as either low or intermediate level are:

1. **The risks associated with the intended use(s) (indications) of the product (e.g. whether incorrect use could lead to the consumer delaying necessary medical treatment).** Nestlé agree that indications which relate to health conditions that are more serious and where incorrect use might, for example, lead to a delay in seeking medical treatment and adverse consequences for the consumer would be unsuitable for low level permitted indications and might be suitable as intermediate level indications.

2. **The intrinsic risk of the product (e.g. the toxicity of its ingredients).** Ingredients for listed medicines must be chosen from a permitted list and quantities of certain ingredients are limited by other regulatory instruments. Choice of ingredients is not a risk factor that needs to be considered in determining if a product is low level or intermediate level.

3. **The risks associated with the quality of the product (e.g. requirements for sterility).** Complementary medicines are required to be made under the code of GMP. There are no differences in the requirements for quality proposed for intermediate pathway products

above the requirements for low level listed products. Quality of the product is therefore not a risk factor that needs to be considered in determining if a product is low level or intermediate level

4. **Whether the indications relate to the treatment of a healthy person, or persons suffering from a disease, ailment or condition.** Low level permitted indications should be suitable for treatment of any disease, ailment or condition that are non-serious and self-manageable. Nestlé agree that if a health condition is serious and where it is likely that delay in seeking medical advice or treatment may be expected to result in an adverse outcome for the patient then this is not suitable for a low level indication.

5. **Whether the indication relates to treatment of a particular target population such as young children.** Target population in itself should not determine if a product should be in the low or intermediate pathway. There are currently in place regulatory instruments that limit the dosage instructions for certain products (e.g. cough cold products not for children under 2 years of age). These should apply equally for low level permitted indications and intermediate level indications and are not a risk factor that needs to be in considered in determining if a product is low level or intermediate level.

From these risks there needs to be a clearly defined categorisation of products into the three proposed categories, noting that the only difference between the proposed low and intermediate pathway is the indication(s) for use of the medicine and that the proposed low level pathway is equivalent to the current listed medicine category and the proposed new level pathway is for higher level indications than are currently permitted for listed medicines.

The descriptions of Intermediate indications are that

1. They <u>will</u> include reference to <u>prevention or alleviation</u> 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).

2. Intermediate indications are <u>generally more definitive</u>, <u>relate to more serious health conditions</u> and incorrect use might, for example, lead to a delay in seeking medical treatment and adverse consequences for the consumer.

3. It is also proposed that indications that reference to a **restricted representation** will be intermediate level indications

There is apparent inconsistency in the definitions of point 1 and 2 above in that forms of a disease or condition for which a new pathway indication is to claim prevention or alleviation of are described as non-serious ones that by their nature are self-limiting, self-diagnosable and/or self-manageable.

However intermediate indications generally relate to more serious conditions where incorrect use of the product or delay in seeking medical treatment might result in adverse consequences of the consumer.

There are no examples given in the consultation document of any diseases or conditions that are naturally self-limiting, self-diagnosable and/or self-manageable but that might lead to adverse consequences for the consumer by incorrect use or delay in seeking medical advice. By this proposed definition of intermediate indications it is not fully clear exactly where the dividing line between low and intermediate indications is in all cases.

Definitive / specific indications.

More specific or definitive indications for use should not in themselves make a product a higher risk and should not be the single determining factor for whether a product has a low level permitted indication or a medium level indication. Claims on medicine labels and in advertising may be very specific or definitive but these are not always part of the indications for use.

More definitive or specific indications should not automatically place a product into the new intermediate pathway.

Definitive or specific claims or indications are currently suitable for listed complementary medicines and therefore should be able to continue to be available for products under the low level permitted indications pathway.

An example is given in the consultation document that making an indication more specific or definitive would turn that indication into an intermediate level indication. In this example the low level pathway indication is **'May help manage symptoms of common cold'.** The intermediate indication is **'improves symptoms of common cold such as sore throat and runny nose within two days'.**

These symptoms and conditions (common cold, sore throat and runny nose) are all suitable to be referred to by low level indications. The action "improves" should be suitable for low level permitted indications. The claim "within two days" is a claim and not an indication, or part of an indication. While a sponsor must hold evidence to substantiate "within two days" this is a claim only and should not form part of the indication for use on the ARTG. A claim such as "within two days" does not form part of the indication for registered OTC medicines and nor should it for complementary medicines.

The example in the consultation document of a medium level indication should be considered as three low level permitted indications plus a marketing claim. Therefore in this example the product should be able to select the three indications, which are currently suitable indications for listed medicines, from the permitted indications list.

Focusing solely on the indications does not take account of what is the overall impression of the product. A combination of the product name, plus indications, plus other claims can be included together on a product label to create an overall impression that is more specific or more definitive than the indications only.

Being more specific or definitive in itself should not move an indication from low level to intermediate level. A more specific or definitive indication may not hold any more risk than a less specific or definitive indication.

A sponsor who wishes to list a medicine for relief of cold and flu symptoms should be able to tell consumers which symptoms of a cold and flu the product relieves without that requiring the product to be listed via the new pathway and requiring a clinical trial to be performed on the actual product. For a cold and flu product not to able to list specifically which symptoms of cold and flu it relieves could be seen as deceptive and misleading and would be detrimental to the interests of consumers and reduce a consumers ability to choose the right product for their needs.

Classifying products as either low level pathway or intermediate level pathway based solely on how specific or definitive the indications are, or by certain small changes to the wording of the indication can be subjective, open to opinion and likely to cause uncertainty and confusion.

Indications that are specific or definitive are currently permitted for listed medicines. The introduction of a new pathway that is above that for currently listed medicines should not be used to introduce new recruitments for some listed medicines which have specific or definitive indications to push them into the new higher level classification.

If more definitive or specific indications are a factor that is going to determine what is, or is not, a low level permitted indication then this will need to be explained very clearly in the permitted / coded indications consultation. Sponsors will also need very clear definitions and unambiguous guidelines that very clearly allow them to know which pathway their products need to use.

Target populations

Nestlé do not support that the target population of a product alone can determine the risk level of the product and whether an indication should use low level permitted indications or intermediate indications pathway. A permitted indications list should contain indications only and there should not be a complete restriction on any age group such as young children.

For products that are currently listed and are suitable for a particular target population then the introduction of a new pathway should not suddenly make those listed products unsuitable for that target population.

There are already warning statements in place for product categories, for example cough cold that may not be indicated for children under 2 years of age without medical advice. The permissible ingredients list can also require label statements restricting use of a particular active ingredient to certain age groups.

There are already available regulatory instruments which place suitable controls on the use of certain active ingredients in products with dosage instructions for young children where it is necessary based on the risk of the ingredient. A blanket restriction on directions for use for all products for certain age groups being permitted for all low level permitted indications is not based on risk.

For all listed medicines the sponsor must certify that the product is safe for its intended use. There are products that are suitable for permitted indications for very young children such as nappy rash cream and probiotics and to require products such as these to be assessed by the intermediate pathway and require clinical trials to be conducted specifically on young children would not be appropriate.

Treatment – prevention - cure

One differentiation proposed between low level permitted indications and intermediate indications is that intermediate indications may use the words "treatment, prevention, alleviation and cure, whereas low level permitted indications may not.

The argument for this from table 6 is that "Treatment, prevention, alleviation and cure have a more definitive meaning which are not suitable for permitted indications as they may lead to a delay in seeking medical treatment and adverse consequences for the patient."

The words treatment, alleviation and prevention themselves in indications will not lead to a delay in seeking medical treatment and adverse consequences for the patient. The risk to the consumer is if the disease, condition or ailment that they have is self-limiting, self-diagnosable and/or self-manageable or not. Singling out some specific words that are 'actions' in the indication is not as important in defining the risk of the disease or condition referenced in the indication.

Words such as treatment, prevention, or alleviation in an indication may be suitable for lower level permitted indications. Rather than focusing on a few select action words and defining them as only suitable for indications for intermediate or registered medicines the risk to the patient of not seeking medical advice should be the determinant of whether an indication is suitable as a low level permitted indication or not.

There are indications where the words prevention or treatment are acceptable for listed medicines and use of these action words should remain permitted for low level permitted indications, provided the sponsor of the product holds suitable evidence. Examples of existing indications and coded indications are:

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.

As these action words such as prevention and treatment are already in the coded indications list and are suitable for listed medicines they should be retained in any permitted indications list when a new pathway is introduced.

There would be no difference in the risk to the consumer and little if any difference in the mind of the consumer between the following indications.

Relieves the symptoms of colds v's alleviates the symptoms of colds. Relieves and alleviates in this context could be considered as synonymous. Alleviates should be a suitable terminology for coded permitted

Prevention implies use by healthy people wanting to remain healthy so products indicated for prevention should be permitted to be listed by the low level permitted indications pathway.

3.4 – 3.5

Approaches to Establishing efficacy.

The evidence for complementary medicines is largely based on published information and studies and most is ingredient based rather than product based. Clinical trials can be extremely costly and difficult to develop and many studies, especially for preventative studies, need to be conducted over a long timeframe with a large number of participants. The results of a single clinical trial is usually not enough to produce meaningful data and often a review and independent assessment of many clinical trials is required to come to a conclusion as to the effectiveness of an ingredient.

The proposed approach for establishing efficacy via the new pathway is unsuitable for complementary medicines. The requirements to supply clinical data by product rather than by ingredient will result in a situation where much of the world wide clinical data generated on complementary medicines will not be usable by a sponsor wanting to establish efficacy via method 1 and products that may become available in many other countries would not be able to be marketed in Australia because of the requirement to only consider clinical data on the actual formulation that is intended to be listed.

Another issue is that only products that can use the proposed method 2 for establishing efficacy are products where the active ingredients are single defined chemical entities. Therefore any herbal or probiotic products that need to be listed via the intermediate pathway are required to provide clinical data on the finished product.

The large cost of clinical trials on each new formulation for these types of products and the length of time that they would need to run to generate suitable evidence is a huge disincentive to use the new pathway. Sponsor of herbal products wanting to list various dosage forms with the same active ingredients or make change to a formulation of a product on the new pathway would need to repeat the same clinical trials multiple times.

Continual repetition of clinical trials on new dosage forms or reformulation of essentially the same herbal product to prove efficacy of each and every formulation is of no value and is out of step with regulation of these types of products internationally. The requirements for clinical trials to be conducted on each new product formulation would result in the new pathway being little used.

For all products, including products with active ingredients such as herbs or probiotics, it should be sufficient to source clinical evidence for each active ingredient, or active ingredient combination from published studies.

For an immediate release product a sponsor should be required to demonstrate that a product has a suitable disintegration or dissolution profile. For herbal products or probiotic products, disintegration should be sufficient if there is not any marker compound of the active ingredient that can be used for a dissolution profile. Demonstration of bioequivalence to another product already on the market is too high a regulatory requirement for such low risk products.

3.6 – 3.8

Evidence requirements

The evidence requirements for the new pathway are too high and inappropriate for complementary medicines based on the risk of the products. The requirement for the first to market for every product, and for all products where the active ingredients are not defined chemical entities to conduct a clinical trial on their actual product is a huge cost and disincentive to using the new pathway.

Demonstration of Bioequivalence to a prescription medicine standard is also not appropriate for a new pathway listed medicine.

4. **Permitted indications:**

Nestlé consider that the criteria for inclusion on the permitted indications list should be that a permitted indication should not make reference to a serious form of a disease or condition. If an indication is for a disease or condition is self-diagnosable, or self-manageable and / or self-limiting then this would be suitable for a permitted indication. Conditions where a delay in seeking medical advice or medical treatment would be detrimental to the consumer would not be suitable for a permitted indication.

Any disease or condition that is currently suitable for listed medicines should therefore be have permitted indications under the new proposed model.

Actions of prevention, treatment, or alleviation should be included on the permitted indications list and sponsors should be able to use these actions in permitted indications when they hold evidence to substantiate the indication.

- Products indicated for “prevention” are likely to be used by healthy people wanting to maintain health.
- The action treatment is non-definitive and in the minds of consumers includes general use of a medicine product.
- Alleviation is synonymous with relief of symptoms of. For example a product for alleviation of pain would be expected to relieve the symptoms of pain, not cure the underlying condition.

Nestlé supports option 2 as the best option for a permitted indications list. With the implementation of any permitted indications list, guidance documents and associated regulations must be developed. Thorough consultation with industry must be conducted in order to produce a comprehensive list of indications and qualifiers.

Nestlé has concerns about adding requirements to the permitted indications list that specify the circumstances when the indication can or cannot be used or specify conditions that must be met where these requirements are already included in other regulatory instruments.

Trying to duplicate requirements into the permitted indications list when they are already in other regulatory instruments, such as the permissible ingredient list, will inevitably lead to inconsistencies

between the different regulations. Only where a requirement is not already included in another regulatory instrument and where it is not possible to be included in another regulatory instrument should a requirement for an indication be included in the permitted indications list.

Having requirements incorporated into the permitted indications list and other regulatory instruments such as the permitted ingredients list and RASML will make navigating the regulatory requirements for listed medicines more complicated and difficult. It also goes against the intention of the permissible ingredients list that was to simplify the range of legislative instruments for listed medicines by capturing all of the ingredients available for use in listed medicines and their requirements in the one instrument.

Non-permitted list

Table 6 indicates that a non-permitted indications list would be created for indications that TGA will have determined are unsuitable for inclusion in the permitted indications list. Nestlé do not support the creation of a non-permitted indications list as it adds an unnecessary level of complexity, and requires updates and maintenance to make sure it aligns with other regulatory instruments.

Indications that are not suitable for the permitted indications list should be adequately controlled by existing regulatory instruments and new guidance documents.

For the examples given in table 6.

- Biomarkers: If any biomarkers are suitable for permitted indications then these will be included in the permitted indications list. An explanation in a guidance document would be sufficient to explain to sponsors that any other biomarkers that are not included in the permitted indications list are considered to be reference to a serious form of a disease and cannot be used.
- Smoking cessation: If smoking cessation is not a suitable indication for low level permitted indications then there will be no indications on a permitted list that a sponsor can select.
- Obesity: Obesity as a serious form of a condition is currently not permitted as an indication in listed medicines and this can be clearly explained in a guidance document without the requirement for a non-permitted indications list.
- Vulnerable populations (e.g. 4 week old infants): This is already adequately controlled by the warning statements required by the permissible ingredients list, which considers the risk of each product type or active ingredient. Age group is not a sole determinant of risk and a blanket requirement should not be introduced that all products with dosage instructions for a particular age group must be listed by the intermediate pathway or registered. Products such as nappy rash treatment would be suitable for a 4 week old infants and requiring all nappy rash products to be listed via the intermediate pathway and submit a clinical trial on the actual product is not commensurate with the risk of the product.

5. Claimers:

Nestlé does not support the use of a claimer in any form for the following reasons.

- Any claimer will likely imply TGA endorsement of the product that carries the claimer.
- A claimer will imply that a product is more effective than other products that do not contain the claimer.
- The claimer is being suggested only for complementary medicines and this is not a level playing field. Consumers seeing a claimer on a complementary medicine may choose that in preference to an OTC medicine that is not permitted to have a claimer. Consumers should be encouraged to choose medicines on the basis of what is the best medicine for them and a claimer that is only permitted on some complementary medicines could be seen to work against that.
- Claimers may not be permitted in other markets, therefore products that are for example, sold in both Australia and New Zealand in the same packaging may not be able to use the claimer on the product label.
- Due to the limited space on labels not all products that are permitted to use the claimer will be able to fit it on the pack.
- As use of the claimer is not mandatory it will not be immediately clear to consumers or competitors if an indication is illegally being used on a product or if the product was approved by the new pathway but the sponsor did not include the claimer on pack.
- If there was use of a claimer it would require an ongoing regular education campaign to make sure that all consumers understand it. Even if there is comprehensive, ongoing consumer education undertaken by TGA to explain the distinctions between the three different levels of regulation within complementary medicines and how this fits into the overall regulation of different types of medicines it seems likely that a large percentage of consumers will still not understand what the claimer means and why it is on some products and not others and why OTC medicines that are assessed for efficacy do not have the claimer.

Rather than having a claimer as a statement or a visual symbol, Nestlé propose that products assessed via the new pathway be given a different listing number that is distinct from the current AUST L / AUST R. The advantages of this are that it will not take up any extra space on a product label. It will be mandatory on all products, it will clearly show that a product has been approved via the new pathway, it will not be seen as TGA endorsement or imply superiority of the product.

6. Incentives for innovation

Protection for new ingredients

Nestlé generally support the proposal to provide market protection to applicants for new ingredients.

There is currently a disincentive to apply for new ingredients to be permitted for use in listed medicines as the applicant must pay the evaluation cost but as soon as an ingredient is approved anybody can use it.

Nestlé considers that the proposed 2 year exclusivity period for use of an ingredient after it has been approved is too short to provide a sufficient incentive to encourage applications for new ingredients. After any new ingredient is approved there is still a considerable amount of time before a new product can be listed, produced, ranged with retailers and brought to market.

If the applicant for a new ingredient is an ingredient supplier then the time to market for a product could be longer as product manufacturers may not consider developing products that use the new ingredient before it is approved.

Nestlé suggest that a longer exclusivity period such as 3 years should be considered.

There should be no reason to restrict applications for new ingredients to only one applicant. Multiple applicants could apply for approval for the same ingredient before any of the applications are approved. In this case once one application is approved other applicants should not be required to withdraw their application.

Within the exclusivity period other applicants should be permitted to apply for approval for an identical or similar ingredient. For complementary medicines much of the information for new ingredients is publicly available and most applications for new ingredients are likely to be for ingredients that are already approved for use in other markets.

Protection for efficacy data

Nestlé agrees with the principle that sponsors who conduct clinical trials on their own formulation should have an exclusivity period in which other sponsors cannot use that clinical trial data for an application by method 2.

Sponsors have 2 options for protection of efficacy data:

Option 1 the sponsor does not publish their clinical trial.

If a sponsor conducts clinical trials on their own product and does not publish the studies then other sponsors should not be able to use this data. The requirements for a sponsor of listed medicines is that they must hold evidence to support the indications for use for their medicine.

A sponsor may not copy a product that is already approved on the market and show bioequivalence data but not submit any clinical data in support of the efficacy of the ingredients.

Therefore if a sponsor conducts clinical trials on their own product and does not publish the clinical trials they have protection for that efficacy data forever, or until such time that the clinical trials are published.

Option 2 the sponsor does publish their clinical trial.

There are benefits to publishing clinical trial data in that the clinical trials are open to peer review and comment. To encourage the publishing of clinical trial data that a sponsor conducts on their own product there should be a reasonable and generous period of exclusivity given to the sponsor so that they can benefit from the investment that they make in conducting and publishing the clinical trial.

To promote innovation and to encourage sponsors to publish any clinical trial data that they produce on their own formulation, Nestlé consider that an exclusivity period of at least 5 years for clinical trial data be given. The data exclusivity period should commence from the date that the product gains approval and is entered onto the ARTG.

If the data exclusivity period is too short it may discourage sponsors from publishing clinical trial data.

One other consideration is how data exclusivity could be granted if the indication is already on the permitted indications list. A sponsor may conduct a clinical trial on their own product in order to obtain evidence to support an indication that is already on the permitted indications list. This could be a situation where the clinical research is used to establish evidence for a new indication for an existing active ingredient.

Sponsors who conduct a clinical trial on their own product in order to produce evidence to substantiate a new indication for an ingredient should have exclusivity of this evidence for that ingredient even if the indication is on the permitted indications list.

7. Transition

Nestlé agree in principle with the duration of the transition period where a sponsor wishes to amend the listing to select only permitted / coded indications. If there are sponsors of products which are currently listed that will be required to perform a clinical trial on their own product formulation in order to submit for approval to maintain that indication via the new pathway then a 3 year transition period appears to be inadequate.

The transition period should only commence once all regulatory instruments and guidance documents are in place including the coded indications and from the time that TGA is ready to accept applications via the new pathway.

Under the transition arrangements it appears that a sponsor could not use method 2 for establishing efficacy if there are no products on the ARTG with the same active ingredients that have been assessed and approved by TGA for the proposed indication. If the first sponsor must supply clinical trial data on their own product to transition to the new pathway then it seems likely that at the end of the proposed transition period of 3 years that very few products, if any, could have been able to receive approval via the proposed new pathway.

Part 2: The background to this consultation indicates that the recommendations of the review are for complementary medicines manufactured, supplied and / or exported from Australia. This suggests that the proposed reforms will apply to complementary medicines that are manufactured in Australia for export only. Nestlé ask for clarification on export only complementary medicines. Will complementary medicines for export only that have indications that are not on the permitted indications list be required to have the indications assessed under the proposed new pathway?