OTC COUGH AND COLD MEDICINES FOR CHILDREN AGED 2-12 YEARS

A SUBMISSION BY THE AUSTRALIAN SELF-MEDICATION INDUSTRY

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Executive Summary

The Australian Self-Medication Industry (ASMI) appreciates the opportunity to respond to the TGA's proposed changes to the availability, labelling, packaging and scheduling of registered OTC cough and cold medicines for use in children aged 2-12 years.

ASMI acknowledges the TGA's extensive investigation and consideration of published data, information provided by sponsors, reports of adverse drug reactions over a 28 year period, and the decisions taken by other regulatory agencies.

ASMI contends that some of the proposed changes are excessive and not justified on the basis of the evidence available. ASMI has made alternative suggestions, which we believe would introduce more appropriate measures for the benefit of Australian consumers and be consistent with the principle of minimum effective regulation.

ASMI accepts the TGA's proposal that OTC cough and cold medicines should not be used for the treatment of children under 6 years of age with the exception of the proposed inclusion of bromhexine and topical nasal decongestants, which have been specifically excluded from these restrictions in New Zealand.

We propose the following alternative wording for label statements for products to be used in the 6 – 12 year age group: "Consult with a health care professional before use in children aged 6 - 12 years", or equivalent wording, in line with the approach being adopted in New Zealand.

ASMI considers that the enhanced labelling we have proposed would provide sufficient additional warning to ensure safe use in consultation with a healthcare professional. Consequently we believe there is no justification for further restrictions through rescheduling. This approach would be in line with arrangements in Canada and the UK.

ASMI suggests that the new requirements should take effect from May 2011. This date takes into account timeframes for changes to manufacturing and the seasonality of the product supply cycle. It is also aimed at avoiding the impost of two sets of changes if NDPSC should recommend scheduling changes.

ASMI believes liquid preparations for application to the eye, ear or mucous membrane when supplied in small containers or fitted with a restricted flow insert should be excluded from the proposed requirements for child-resistant packaging as detailed in TGO 80. Implementation of child-resistant packaging for other cough and cold medicines should occur from May 2011, with longer timelines where necessary, in consultation with the TGA.

ASMI commits to working with the TGA and other stakeholders to assist in the development and delivery of appropriate educational messages about the use of cough and cold medicines in children to ensure the quality use of medicines.

1. Background

Regulatory authorities in the USA, Canada, the United Kingdom, New Zealand and Australia have reviewed the safety and efficacy of OTC cough and cold medicines for children under 2 years of age and concluded that these medicines should not be used for children in that age group. Regulatory and voluntary actions were taken and labelling changes were made to enforce these conclusions.

Subsequently, the focus of review has extended to the use of cough and cold medicines for the treatment of children aged 2-12 years.

The TGA is now proposing significant changes to the availability, labelling, packaging and scheduling of registered OTC cough and cold medicines for use in children.

The medicines reviewed and potentially affected by the regulatory actions being considered contain one or more of 21 substances in the categories Antihistamines, Antitussives, Expectorants/Mucolytics and Decongestants. In addition, the TGA later added senega and ammonia to the list of substances.

2. The Australian Situation

As part of the review process in Australia, the TGA engaged two experts to conduct an external review of the available safety and efficacy data for registered OTC cough and cold medicines for children marketed in Australia, as published in the medical literature and supplemented with additional information provided by sponsors of cough and cold medicines. The resulting report (External Report) was considered by a TGA internal panel, together with additional safety data from TGA records, and by the Medicines Evaluation Committee (MEC).

According to the External Report, MIMS identifies over 130 products in the category expectorants, antitussives, mucolytics and decongestants which are available in Australia. Doses for children aged less than 12 years are supplied on the labels of more than 70 of these medicines, which are mostly scheduled as S2 (pharmacy medicines). After recent changes, all sedating antihistamines are now S4 drugs when used in children aged less than two years.

Problems in the US with the use of cough and cold medicines in children related to misuse, medication error, accidental overdose, accidental exposure and concurrent use of multiple products, rather than consequences from usage in accordance with the directions.

The External Report points out that the presentation and availability of cough and cold medicines overseas is very different from the situation in Australia. The US has a far greater range of products, with a greater range of "actives" and a greater range of combination products. In the US, cough and cold medicines are generally available without any requirement for "pharmacy only" sale or "pharmacist advice", which is an intrinsic feature of Australian drug regulation and is widely considered to be a valuable feature. Recommendations against use in children aged <2 years has applied to far more products in Australia, until very recently.

As noted in the External Report, records of death with possible attribution to poisoning have been kept in the US for more than 50 years, long before the advent of child resistant-packaging both for liquid and solid forms of drugs. Information based on former decades is now being used to suggest excess mortality from cough and cold medicines, and this information may not altogether reflect the current situation in the US, and even less the situation in Australia.

3. Basis for the Australian Recommendations

Cough and cold products have a long history of safe use in Australia in both adults and children. Many products on the market today have been available and used safely for more than 30 years.

According to the External Report, the external reviewers and the TGA decided to use a broad search strategy in reviewing the literature, because of the overlap of the use of drugs for coughs and colds and other conditions, in order to obviate as far as possible missing important references. All abstracts provided by the TGA and all references from Cochrane reviews were read and relevant articles were reviewed in full text. Additional articles were read and referenced as appropriate in the final review to clarify efficacy and toxicity of the drugs. A summary for each drug and/or drug class was included in the External Report.

The external reviewers interpreted safety to include adverse effects of the medicines, either single drugs or a combination of drugs, of any severity i.e. from minor, to death, in recommended dosages, but including also in non-intentional overdose where this is common. They interpreted efficacy to relate to effectiveness of relief of cough and other symptoms of the common cold, in accord with the label claims of cough and cold medicines sold for use in children.

The TGA internal panel report (Internal Report) summarised the key findings of the External Report as follows:

> (i) There is currently a strong demand for OTC cough and cold medicines for the treatment of children and that demand has been regarded as evidence of their effectiveness.
>
> (ii) The available clinical data does not support the efficacy of these medicines in children.
>
> (iii) The use of these medicines in children has been the cause of significant adverse reactions, including death.

In our view, this summary does not adequately reflect the observations and conclusions reached by the external reviewers in the External Report.

In particular, in relation to safety, the external reviewers considered data about poisonings in Australia and stated that "death or serious injury from children's cough and cold medicines is vanishingly rare". They noted that, although there are substantial numbers of calls to Poisons Centres in regard to these drugs, very few are considered to be serious enough to refer for assessment and treatment.

The External Report stated that it is possible to make definite conclusions about the safety of cough and cold medicines in children as follows:

> - Generally, these medicines are very unlikely to be harmful in label dosages, and in non-intentional overdose in the typical 1-2 year old age group, serious poisoning is rarely seen.
>
> - A recent study in the United States demonstrated that OTC cough and cold preparations were only present in toxicology screens in 5% of life-threatening poisonings in children.
>
> - This may not apply to some drugs in adult doses in solid form, but this is not going to be influenced by any changes that might be made in the nature or availability of cough and cold medicines for children.
>
> - Overseas reports of serious poisoning including deaths from cough and cold medicines are generally not reflected in current Australian experience. Documentation of such deaths is often confounded by co-existing severe illness, multiple drug administration, solid drug forms, the possibility of homicide and other factors.

The External Report then made a few more specific comments about several agents.

In relation to efficacy, the External Report concluded that it is impossible to make a general statement on the efficacy of cough and cold medicines for children. The external reviewers observed that there are relatively few high quality studies of efficacy of these medicines that include children, and extrapolation from adult studies is of limited value. They then endeavoured to "discuss probabilities and to inform decision-making, in regard to at least some of the commoner drugs and combination products".

3.1 Sufficiency of evidence

3.1.1 Evidence of safety

As noted in the External Report, there has been ample time for post-marketing surveillance, and the adverse effects of drugs used in cough and cold medicines are generally well known, both in normal use and over-dosage.

Mild, reversible side effects of cough and cold medicines are well known and well described in standard references such as Martindale, as might be expected for drugs which have been in use for decades.

There is no evidence in the Australian market suggesting patterns of misuse, either intentional or accidental. Those products that could potentially be abused are only available in pharmacy which provides a level of restriction on availability, along with access to advice from a health care professional.

In addition to the External Report, the TGA has prepared an analysis of reports of suspected adverse drug reactions (ADRs) to cough and cold medicines used for the treatment of children in Australia.

According to data held by sponsors, the average occurrence of adverse events in children from data held by sponsors indicates that there is less than 1 event in every 287,000 units sold or 0.0003% of sales.

Over a period of 28 years (1981-2009) the TGA has received 99 reports of suspected ADRs in children under the age of 12 associated with cough and cold. 14 ADRs were classified as serious (1 probable causality, 10 possible, 3 unclear). 12 of the serious ADRs occurred in children under 6 years.

In addition, two reports of accidental overdose and two reports of intentional overdose were also received.

The TGA has not provided a breakdown of the pattern of reports by year.

Despite these data revealing only 1 ADR with a probable causal relationship with the use of cough and cold medicines in Australia, in a child under 12 years of age over a 28 year period, and another 10 possibly-related ADRs, the TGA refers to "the historical profile of ADRs in Australia and overseas" in making its recommendations and determining that the risks relating to the use of cough and cold medicines in children outweigh the benefits.

In ASMI's view the conclusions reached by the TGA have not been justified.

3.1 2 Evidence of efficacy

The External Report states:

Both internationally and within Australia, there is a strong emerging viewpoint that drugs should not be used in children without study of efficacy, safety and pharmacokinetics done specifically in children of the age-groups likely to receive those drugs. Applied broadly, this would deprive children of many useful drugs currently used for children, as well as new drugs as they become available. In the current context, the lack of studies done in children is a constantly-recurring feature.

The external reviewers considered three Cochrane reviews that are relevant to the current deliberations. Two of these are currently described on the Cochrane website as being "withdrawn" (6 December 2009). The most recent Cochrane review - Smith SM, Schroeder K, Fahey T. Over-the-counter medications for acute cough in children and adults in ambulatory settings. Cochrane.Database.Syst.Rev. 2008; CD001831 – is readily available and contains several very pertinent observations. This Cochrane review considered randomised controlled trials comparing oral OTC cough preparations with placebo in children and adults suffering from acute cough in ambulatory settings, and noted all cough outcomes and adverse effects. The results in children were summarised as follows:

Antitussives (two studies), antihistamines (two studies), antihistamine decongestants (two studies) and antitussive/bronchodilator combinations (one study) were no more effective than placebo. No studies using expectorants met our inclusion criteria. The results of one trial favoured active treatment with mucolytics over placebo. One trial tested two paediatric cough syrups and both preparations showed a 'satisfactory response' in 46% and 56% of children compared to 21% of children in the placebo group.

The Cochrane reviewers concluded:

There is **no good evidence for or against** the effectiveness of OTC medicines in acute cough [highlighting added]. The results of this review have to be interpreted with caution due to differences in study characteristics and quality. Studies often showed conflicting results with uncertainty regarding clinical relevance. Higher quality evidence is needed to determine the effectiveness of self-care treatments for acute cough.

Thus, the Cochrane reviewers did not conclude that cough and cold medicines were ineffective. They concluded that there is insufficient evidence for or against their effectiveness which meets the standards and criteria applied by the Cochrane review.

Similarly, in the External Report, the external reviewers note that there is an undoubted strong demand for cough and cold medicines for children, interpreted by some as evidence of efficacy, and state that they do not agree with this interpretation, but there is **no evidence to refute or support** the idea [highlighting added].

This, we feel, is the nub of the problem facing sponsors of cough and cold medicines in Australia, as well as the TGA. OTC cough and cold medicines, in common with many other existing therapeutic products, were "grandfathered" when the new national regulatory system was introduced in Australia in 1991, on the basis that they met the criteria in place prior to the introduction of the new requirements. Products have only been required to retrospectively meet new requirements if there have been justifiable grounds to do so.

In ASMI's view, the TGA has not produced clear evidence that there is a significant problem in Australia caused by the use of cough and cold medicines in children which provides sufficient grounds to justify the proposed new requirements.

3.2 Comparability with overseas requirements

3.2.1 Overseas recommendations relating to safety and efficacy

The TGA states that its proposed requirements would bring the regulation of cough and cold preparations in Australia into line with measures in place in the UK and Canada.

This is not completely accurate.

In the UK the Medical Healthcare products Regulatory Agency (MHRA) has stated that a list of 15 substances used in cough and cold medicines should be contraindicated in children under 6 years and requires strengthened warnings for products for children 6 to 12 years containing the substances reviewed.

Health Canada has stated that a list of 13 substances used in cough and cold medicines should not be used in children under 6 years of age, and requires a statement to this effect. It does not require a statement advising that the product should only be administered to children between the lowest specified age and 12 years on the advice of a doctor or pharmacist, as proposed by the TGA, but requires a statement about consultation with a health care professional in specified circumstances.

We also note that, in New Zealand, Medsafe has stated that a list of 12 substances used in cough and cold medicines should not be used in children under 6 years, and specifically excludes bromhexine and topical nasal decongestants from this restriction. All medicines indicated for the treatment of the symptoms of the common cold containing only bromhexine or topical nasal decongestants (oxymetazoline, xylometazoline, and intra-nasal phenylephrine) remain contraindicated in children under two years of age.

Bromhexine and the topical decongestants were based on the lack of evidence of toxicity of bromhexine and less evidence of harm in relation to the topical decongestants. The labelling of the 12 restricted cough and cold medicines will require a statement about consultation with a health care professional before using these products in children aged 6 years and over.

ASMI considers that there is an important difference between the Australian proposal that advising that the product should only be administered to children between the lowest specified age and 12 years "on the advice of a doctor or pharmacist", and advice that the consumer should consult a health care professional before using these products in children aged 6-12 years. The former reads as if the health care professional must take the initiative in making the recommendation (and would correspond with the S3 rescheduling proposal below), whereas a statement on the label to consult a health care professional would correspond with S2 scheduling and enable the consumer to take the initiative in selecting the product.

We also note that, in the US, members of the Consumer Healthcare Products Association (CHPA) have voluntarily agreed to label relevant products as being suitable only for children aged 4 years and older, prior to any FDA policy announcement. In addition, a study of 8 cough and cold substances representing about 95% of the cough and cold paediatric market is to be undertaken to provide data on safety and efficacy in children, and is expected to be completed in 2011.

It should also be noted that bromhexine was not included in the reviews undertaken in the UK, Canada and the US.

3.2.2 Overseas recommendations relating to packaging

The TGA proposes that all OTC cough and cold medicines should be marketed in containers with child-resistant closures, and states that this would bring the packaging of cough and cold preparations in Australia into line with measures in place in the UK and with recommendations made by the regulators in the USA.

This is not completely accurate.

The MHRA has stated that all liquid cough and cold products containing the ingredients reviewed should be supplied in a child resistant container, but has specified that topical preparations, including nasal sprays and drops and throat sprays, are excluded from this requirement.

We understand that the US approach will also be to require child-resistant packaging only for oral liquid cough and cold medicines.

3.2.3 Overseas recommendations relating to availability

The MHRA has stated that cough and cold medicines for 6-12 year olds containing the substances reviewed will in future be available only through pharmacies. This will bring the arrangements in relation to gauphenecin, ipecacuana, oxymetazoline, phenylephrine and xylometazoline in line current Australian arrangements.

If the TGA were to require paediatric cough and cold medicines to be sold in Australia as S3 (pharmacist only) rather than S2 (pharmacy only), this would exceed the restrictions being introduced in the UK, as there is no such additionally-restricted category in the UK.

Health Canada has not made changes to the classification of medicines for use in children 6 – 12 years where these products are supplied in line with S2 supply in Australia.

4. ASMI's Suggested Alternatives

a) Safety, efficacy and availability

As stated in the Internal Report, the risk/benefit ratio of cough and cold preparations is difficult to ascertain. As stated in the External Report, it is impossible to make a general statement about the efficacy of the 21 cough and cold medicines for children which they reviewed, and death or serious injury from children's cough and cold medicines is vanishingly rare.

ASMI notes that 12 of the 14 suspected ADRs reported to the TGA over a 28 year period which were considered to be serious (1 probable, 3 possible and 3 unclear) were in children under 6 years of age.

In view of this, and the recommendations made overseas, we accept the TGA's proposal that OTC cough and cold medicines should not be used for the treatment of children under 6 years of age and, therefore, that the labelling of OTC cold medicines should not include dosage instructions for children under 6 years of age, with the exception of the proposed inclusion of bromhexine and topical nasal decongestants, which have been specifically excluded from these restrictions in New Zealand. The exclusions were based on the lack of evidence of toxicity of bromhexine and the small number of reported adverse reactions involving topical nasal decongestants compared to oral decongestants. Medicines indicated for the treatment of the symptoms of the common cold containing only bromhexine or topical nasal decongestants remain contraindicated only in children under two years of age.

We also do not agree with the proposed statement that "the product should only be administered to children between the lowest specified age and 12 years on advice of a doctor or pharmacist".

Instead, we suggest that the labelling for products containing these medicines should state, "Consult with a health care professional before use in children aged 6-12 years", or equivalent wording, in line with the approach being adopted in New Zealand. The cautionary statement should be placed at the beginning of the directions for use in this age group or under the "Ask your doctor" subheading of performance-based labelling.

Therapeutic Goods Order (TGO) 69A, which amends TGO 69 "General Requirements for Labels for Medicines", states:

> For non-prescription medicines, the aim is that the information on the label is presented in such a way that consumers can:
> a. choose an appropriate medicine on their own;
> b. use the medicine safely and effectively;
> c. readily find the information they need, understand it and act on it appropriately; and
> d. access further information, if they want to know more about the medicine.

ASMI considers that the suggestions we have made would appropriately fulfill these requirements.

ASMI agrees that the need for such limitations on use in children should be reviewed if and when robust efficacy data becomes available.

b) Packaging

TGO 80 "Child-Resistant Packaging Requirements for Medicines" requires most of the medicines in OTC liquid cough and cold preparations to be in child-resistant packaging (CRP). Subsection 7(d) of TGO 80 exempts liquid preparations for application to the eye, ear or mucous membrane (which includes the nasal cavity) when supplied in a container with a nominal capacity of not more than 20 mL or which is fitted with a restricted flow insert.

As noted above, the MHRA has required only that all liquid cough and cold products containing the ingredients reviewed should be supplied in a child resistant container, and have specified that topical preparations, including nasal sprays and drops and throat sprays, are excluded from this requirement.

Therefore, ASMI does not agree that all OTC cough and cold medicines should be marketed in containers with child-resistant closures but, rather, suggests that the current exemptions under subsection 7(d) of TGO 80 continue to apply.

c) Scheduling

The current scheduling of most cough and cold medicines as S2 (pharmacy only) medicines ensures that advice is available from the pharmacist and is in line with the recommendations made overseas. The new arrangements in the UK mean that all cough and cold medicines for children will in future only be available from pharmacies which will bring it in line with current Australian and Canadian arrangements. It is also very important that the scheduling of OTC cough and cold medicines in Australia continues to be aligned with the requirements in New Zealand.

ASMI considers that the enhanced labelling we have proposed for products labelled for use in children 6-12 years, to consult with a health care professional before use in children of this age - except for bromhexine and topical nasal decongestants - would provide sufficient additional warning in relation to the use of these in this age group

If the TGA decides to proceed with its proposal to ask NDPSC to consider including substances used in cough and cold medicines in Schedule 3 when intended for use in children aged 6-12 years, ASMI would argue against this proposal. For reasons noted above, ASMI does not consider that upscheduling is justified.

In addition, sponsors of cough and cold medicines would need to consider whether to introduce a duplicate range of products for consumers above 12 years, which could remain in the current schedules, with attendant costs to sponsors in both manufacturing and marketing, flow-on effects for pharmacy in stock management, and potential issues if consumers decided to purchase these products and use them for children without being guided by appropriate directions for use on the label.

d) Public awareness

ASMI supports the quality use of medicines. The enhanced we have proposed, combined with the communication of clear, consistent messages to consumers and health care professionals, will ensure appropriate use. As has been stated in previous education campaigns, cough and cold medicines are intended for short-term use only and for symptomatic relief of self-limiting conditions.

ASMI agrees that any changes would need to be widely promoted and explained to medical practitioners, pharmacists, parents and caregivers. In particular, ASMI considers that it would be very important to emphasise the long history of safe use of cough and cold medicines in Australia, both in adults and in children and to avoid causing undue concern or alarm by citing data relating to overseas use in circumstances where presentation and availability have been very different from the practice in Australia.

ASMI would be pleased to work with the TGA and other stakeholders to assist in the development and delivery of appropriate educational messages about the use of cough and cold medicines in children.

5. Timing of Changes

ASMI considers that the changes proposed must be implemented in a reasonable fashion, especially given that there is no evidence of patterns of misuse, either intentional or accidental, or serious injury to children in Australia caused by current use of cough and cold medicines.

5.1 Introduction of enhanced labelling

Labelling changes take on average approximately 9 months to introduce to the market, from a final decision being communicated to manufacturers until the manufacture and distribution of finished product with the new labels.

The TGA consultation concludes on 18 December 2009, and so ASMI anticipates that the earliest time that a decision will be communicated is February 2010. It would not be possible for products with the new labels to be distributed to pharmacy in time for the 2010 cough and cold season.

As well, if the TGA proceeds with its current intention to ask NDPSC to consider the rescheduling of cough and cold medicines in children under 12 years of age, the time frame would be even further extended.

Given the need to foreshadow topics for consideration by NDPSC to allow consultation, ASMI calculates that a proposal to reschedule cough and cold medicines for children could not be considered at the earliest until the June 2010 NDPSC meeting, with an effective date for SUSDP amendment of 1 January 2011.

ASMI considers that it would be unreasonable for the TGA to require manufacturers to introduce one set of label changes after the TGA's initial decision was communicated and then a second set of label changes if the NDPSC determined that rescheduling should occur.

The NDPSC's initial decision and its record of reasons would be known in mid-August 2010, with the final NDPSC decision being made at the October 2010 NDPSC meeting.

ASMI therefore suggests that, to accommodate the time frames required for both the TGA and the NDPSC decisions, the requirement for sponsors to manufacture and distribute products with the new labels should take effect from May 2011.

This would be in time for the 2011 winter (the cough and cold season) and would be in line with the recommendations made by Medsafe in New Zealand, thereby taking into account the dual labelling for Australia and New Zealand that exists for many of these products.

5.2 Introduction of additional child-resistant packaging

Child-resistant packaging can take several years to be implemented, due to the manufacturing issues, testing and evaluation required. It is simply not possible to market all OTC cough and cold medicines in containers with child-resistant closures from 1 July 2010.

Instead, ASMI considers that child-resistant packaging should be required to be introduced for OTC cough and cold medicines - with the exclusion of liquid preparations for application to the eye, ear or mucous membrane when supplied in small containers or fitted with a restricted flow insert, as detailed in TGO 80 – from May 2011, although there may be individual circumstances where longer timelines may be necessary, in which case sponsors should comply within a reasonable timeframe, in consultation with the TGA.

6. Conclusion

ASMI does not agree with some of the proposed changes and has, therefore, made alternative suggestions, which we believe would introduce more appropriate measures for the benefit of the Australian consumers without imposing unjustified costs and restrictions on the sponsors of OTC cough and cold medicines for children in Australia.
ASMI stands ready to work with the TGA implement evidence-based measures to ensure the continued safe use of these products by Australian consumers.