



**Australian Government**  
**Department of Health and Ageing**  
**Therapeutic Goods Administration**

## **Summary of actions taken by the TGA and other regulatory agencies regarding cough and cold medicines in the treatment of children**

*October 2009*

The following is a summary, in chronological order, of the key actions taken by the TGA and its four overseas counterparts along with the published rationales for those actions.

### **a. The TGA**

At its June 2007 meeting the Australian National Drugs and Poisons Scheduling Committee (NDPSC) considered the safety record and scheduling of sedating antihistamines with regard to their use in cough and cold medicines for the treatment of children and concluded that the sedating antihistamines promethazine and trimeprazine posed a particular risk to children aged under 2 years and as such should only be available as (S4) prescription medicines to this age group rather than as (S3) pharmacist only medicines, regardless of the presence of a sympathomimetic decongestant. The NDPSC concluded that there was currently insufficient evidence to consider that this risk applies to the remaining sedating antihistamines available. As a result, the Schedule 3 entries for promethazine and trimeprazine were amended to exclude preparations for the treatment of children under 2 years of age.

The Committee also agreed to foreshadow individual consideration of the non-phenothiazines (brompheniramine, chlorpheniramine, dexchlorpheniramine, diphenhydramine, doxylamine, pheniramine and triprolidine) at the February 2008 NDPSC Meeting to allow additional time for the regulator and sponsors to provide further information, particularly data supporting the safety and efficacy in children under 2 years of age.

At its February 2008 meeting the NDPSC considered the available evidence as well as relevant regulatory developments in the USA. The Committee noted that there was a lack of evidence for the efficacy of these products in young children but their use was associated with serious side effects. The Committee recommended that cough and cold medicines containing non-phenothiazine sedating antihistamines become S4 (prescription-only) medicines when in oral medicines for the treatment of children under 2 years of age. The recommended rescheduling of these drugs became effective on 1 September 2008.

At its February 2008 meeting the Medicines Evaluation Committee (MEC) discussed the US developments regarding the use in young children of cough and cold medicines containing antihistamines and the TGA's preliminary assessment of the situation in Australia as compared with the USA. The Committee noted that there were significant differences in the availability and usage of these products in the USA and Australia. In the USA they were available as general sale medicines in supermarkets, etc, and the problems appeared to be the result of misuse, medication error, accidental overdose, accidental exposure and concurrent use of multiple products, rather than on-label usage. In Australia these products were available only through pharmacies and the labelling specifically warned against use in children aged under 6 months.

The Committee was advised of the NDPSC's and TGA's ongoing consideration of the situation and was advised that the TGA was considering a requirement to include the advice, "Do not use in children under two years of age", on the labels of paediatric cough and cold medicines and would also be considering the use of cough and cold medicines in older children. The Committee endorsed the approach being taken by the TGA, and agreed that the use of the advice, "Do not use in children under 2 years of age", should be required on labels of OTC cough and cold medicines.

In March 2008, following the NDPSC decision and MEC advice, the TGA acted promptly and advised Australian sponsors of cough and cold medicines containing sedating antihistamines and approved for use in infants that these products were to become prescription only medicines and issued a formal directive under Section 28 of the Therapeutic Goods Act 1989 that these products must be labelled with an instruction "Do not use in children under 2 years of age". Unless appealed against, this directive would become effective 28 days from the date of the letter. No appeals were lodged.

In April 2008 the TGA issued a public statement (see <http://www.tga.gov.au/media/2008/080409cold.htm>) advising consumers that it had determined that OTC cough and cold medicine containing any of a list of antihistamines, antitussives, expectorants and decongestants should not be used in children aged under 2 years and provided information for parents and caregivers about the safe use of these medicines in children aged two years and older.

The TGA also wrote to doctors and pharmacists advising them that cough and cold medicines containing any of a list of antihistamines, antitussives, expectorants and decongestants should not be used in children aged under 2 years and provided advice about the use of these medicines in children aged two years and older.

In April 2008 the TGA, while having maintained a close watching brief on reviews and regulatory actions by its overseas counterparts, decided to carry out its own independent review of the safety and efficacy of all OTC cough and cold medicines for use in children aged 2-12 years of age. There are currently about 300 such products registered in Australia and these contain one or more of 21 different active ingredients. Almost all of these drugs have been used in Australia for many years and were grandfathered onto the ARTG in 1991 rather than being formally evaluated for safety and efficacy through the TGA's current evaluation processes.

To this end, the TGA carried out a computer-assisted search of the relevant medical literature and identified over 400 research papers and reviews of possible relevance to the review. The TGA also arranged for two external medical experts to carry out an independent assessment of all of the information gathered from the literature search and that submitted by sponsors.

At its April 2008 meeting the MEC was updated on overseas developments regarding the use of OTC cough and cold medicines in children and was advised of actions taken or planned by the TGA.

In April-May 2008 the TGA advised sponsor companies that it was conducting the review, provided them with a copy of the reference list, and asked for comments and any additional data relevant to the review.

In June 2008 the TGA instructed all sponsors of OTC cough and cold medicines not containing sedating antihistamines to commence amending their labelling for all cough and cold medicines to include the warning "Do not use in children under 2 years of age" (unless they already carried a warning to that effect) and to ensure that the change was implemented by mid-June 2009. It is not practical to make such changes to labelling rapidly and, consequently, companies were given one year to comply. There would then be a phase-in period during which existing stock in wholesale and retail outlets was used up and product with the new labelling took its place.

In July 2008 the TGA's two external reviewers commenced their review of the data. The first step was for them to examine the abstracts and reviews and to identify to the TGA those papers on the reference list that were relevant and for the TGA to obtain copies of the full papers concerned.

At the same time sponsors were preparing and submitting additional information and copies of published papers. It took about 2 months for all of the relevant information to be obtained. A total of 9 submissions were received.

Note that a number of Senega and Ammonia cough medicines were 'grandfathered' onto the ARTG as registered medicines, but senega and ammonium bicarbonate are not actually scheduled medicines in Australia. Therefore, in July 2008 the TGA wrote to Australian sponsors of products containing Senega and Ammonia (as ammonium bicarbonate) separately and requested copies of the labelling, quality control specifications and representative batch analytical data for these products and also evidence to support the indications/claims (clinical efficacy) for senega and ammonia mixture as an expectorant.

Responses were received from 2 sponsors of senega and ammonia products. Both sponsors stated that they had been unable to locate any controlled clinical trial data to support the efficacy of senega and ammonia but provided other arguments, including their safety record and popularity to support the continued use of this old medicine in the admitted absence of specific evidence of efficacy.

In September 2008 hard copies of all of the relevant literature references and the sponsor submissions had been obtained by the TGA and copies of these documents were sent to the external evaluators for their consideration.

In December 2008 the TGA's external evaluators submitted their draft report. This draft report was reviewed by the TGA and the evaluators were asked to make some editorial amendments to their report and to add tables summarising the key clinical studies discussed in the text of the report.

In April 2009 The TGA's external consultants submitted their finalised report on their review of the published literature and additional information provided by Australian sponsors relating to the safety and efficacy of all cough and cold medicines when used in children aged 2-12 years of age.

The consultants also provided as an appendix to their report their assessments of the additional information, arguments and comments provided (mostly as "**commercial in confidence**") by the Australian sponsors. The appendix itself, contains in summary form much confidential information from sponsor submissions, and therefore must be treated as **confidential**.

The additional material provided by sponsors did not convince the consultants that their overall conclusion from their review of the open literature that there is no convincing evidence of efficacy of cough and cold medicines in children was inappropriate or required revision.

In May 2009 the TGA completed an analysis of the reports it had received of adverse drug reactions to cough and cold medicines used for the treatment of children in Australia. That analysis is included in the main body of this report.

## **b. The TPD**

In October 2007 Health Canada's Therapeutic Products Directorate (TPD) issued an Advisory (see <[http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/\\_2007/2007\\_147-eng.php](http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2007/2007_147-eng.php)>) that cough and cold medicines should not be used in children under 2 years of age except on the instruction of a healthcare practitioner and being careful to read the label and follow the directions on the label.

In November-December 2008 the TPD issued a record of proceedings from 20 March 2008 of its Advisory Panel on Nonprescription Paediatric Cough & Cold Medications (see <[http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/sci-consult/pediat/sapnppcm\\_gcsmvltr\\_m-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/sci-consult/pediat/sapnppcm_gcsmvltr_m-eng.php)>), as well as a public advisory, information sheet and notice to sponsors regarding oral cough and cold medicines containing any of a lengthy list of first generation antihistamines, antitussives, expectorants or decongestants and the TPD's decisions that these medicines should not be used in children under 6 years of age and that the labelling must be amended accordingly.

The Advisory Panel had concluded that there was no substantive evidence that these drugs were beneficial for the treatment of children aged under 2 or children aged 2 to under 6 and that serious harm was associated with the use of these drugs in both age groups. Furthermore, there were inadequate pharmacokinetic or other data to support any dosage regimen for these drugs. The Panel's Record of proceedings also states:

*"The Panel also noted that the vast array of children's nonprescription combination cough and cold products on the Canadian market, with their numerous combinations of the various ingredients and ingredient categories, is confusing to the consumer and predisposes to medication errors. Should combination products eventually be shown to have therapeutic benefit in children, clear unit doses for each ingredient will need to be established so that dosages can be standardized across product lines. Analgesics were not seen as suitable for inclusion in children's nonprescription combination cough and cold products."*

In its Information sheet, the TPD stated:

*"Cough and cold medicines have a long history of use in children; however, there is limited evidence supporting the effectiveness of over-the-counter cough and cold medicines in children. This is partly due to the fact that for many years it was assumed that cough and cold medicines worked the same way in children and adults. Therefore, the products for children were approved based on estimations from studies on adults. However, there is a better understanding now of how the ingredients found in cough and cold medicines can behave differently in children than adults.*

*Reports of misuse, overdose and rare but serious side-effects have also raised concerns about the safety of these products in children. While the link between the adverse events and the products cannot be definitively proven by these reports, they are signs that Health Canada cannot ignore.*

*Based on a preliminary analysis of available information, Health Canada recommended in October 2007 that over-the-counter cough and cold medicines not be used in children under the age of 2, unless directed to do so by a health care practitioner. Since that time, Health Canada has completed its analysis, received input from a Scientific Advisory Panel convened in March 2008, and decided that certain non-prescription cough and cold medicines should not be labelled for use in children under 6.*

*There were several other factors that Health Canada took into consideration in determining age 6 to be the cut-off for use of these medicines, such as:*

- *Recommendations from Canadian and international health professionals and experts that these medicines should not be used in children under 6;*

- *Body weight and its effect on how medicines work. Some children between the ages of 2 and 6 years may weigh the same as other children who are less than two years old, the most vulnerable group;*
- *Children under the age of 6 years generally have more colds compared to older children and therefore, are likely to be exposed more frequently to these medications; and*
- *Younger children are less likely to be able to communicate a potential side-effect from a cough and cold medicine and to ask their parents/caregivers for help in the same way a child over the age of 6 can.*

*As a result of Health Canada's decision, the labelling of cough and cold medicines for use in children must be changed by fall 2009 to say they should not be used in children less than 6 years of age. These products will also require enhanced labelling for children aged 6 to under 12, child resistant packaging, and the inclusion of dosing devices for all liquid formulations. Since many of the cough and cold medicines currently on the market for use in children under 6 also have instructions for older children and adults, products will still be available to these groups while the new labelling standard is being put in place. As a result, parents or caregivers should consult a pharmacist or a health care practitioner when buying or using these products during this cough and cold season. These medicines can still be used in children 6 and older, and adults. Medicines with dosing information only for children under 6 years of age are to be removed from the Canadian market by fall 2009 as well.*

*Health Canada also recognizes that children's doses should consider body weight, as was concluded by the Science Advisory Panel. Therefore, Health Canada is seeking additional scientific information to help determine the most appropriate dosing for children, and will require children-specific efficacy data with future submissions for children's cough and cold medicines. Health Canada intends to use the information from these studies to further revise the labelling standard.*

In its Notice to Market Authorization Holders the TPD states:

*“By Fall, 2009, the outer and inner labels for all the products will be required to carry advisory information and directions for use such as:*

- *Do not use this cough and cold product in children under 6 years of age.*
- *Keep out of reach and sight of children.*
- *Do not exceed the single and maximum daily dose and duration of use recommended. Higher doses may result in serious harm.*
- *Do not use for longer than 7 days.*
- *Do not give with any other cough and cold medications since serious harm may occur.*
- *To temporarily relieve the symptoms of the common cold.*
- *For liquid formulations the following statement should be included with the directions of use: "Use only the measuring device provided."*
- *Read the complete label [and package insert if applicable] prior to use and follow all label instructions.*
- *Consult a healthcare practitioner prior to combining with other medications, including natural health products, prescription drugs or nonprescription drugs.*

In February 2009 the TPD issued a Final Guidance Document: Nonprescription Oral Paediatric Cough and Cold Labelling Standard (see <[http://www.hc-sc.gc.ca/dhp-mps/alt\\_formats/hpfb-dgpsa/pdf/prodpharma/pedlsc\\_pednecr-eng.pdf](http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/pedlsc_pednecr-eng.pdf)>) which sets out that agency's requirements for labelling (including the acceptable indications, dosage, warnings) for cough and cold medicines containing one or more of a list of 13 drugs substances for use in children aged 6 to under 12 years. The document does not cover the labelling of these medicines for use in children 12 years and older or for use in adults.

The TGA has obtained from the TPD a **confidential** copy of the Summary Report on its review of safety and efficacy data that led to that agency's decision to issue the above advisory and notice. This document is confidential to the TGA may only be viewed by TGA personnel.

### **c. The FDA**

In October 2007 the USA the Consumer Healthcare Products Association (CHPA), on behalf of manufacturers of OTC cough and cold medicines, announced (see <[http://www.chpa-info.org/pressroom/10\\_11\\_07\\_OralInfantMedicines.aspx](http://www.chpa-info.org/pressroom/10_11_07_OralInfantMedicines.aspx)>) that such oral medicines which refer to "infants" would be voluntarily withdrawn from the US market. The CHPA stated that these medicines were safe and effective when used as directed, but were being withdrawn (in consultation and with the FDA and with the FDA's agreement) because there had been "rare patterns of misuse leading to overdose recently identified, particularly in infants" and that safety was the CHPA's top priority.

In January 2008 the FDA issued a Public Health Advisory stating that it had completed a review of the safety of OTC cough and cold medicines in infants and children under 2 years of age and that it was recommending that cough and cold medicines not be used to treat children under 2 years of age because serious and potentially life-threatening side effects can occur. The FDA also strongly supporting the actions taken by the pharmaceutical industry to voluntarily withdraw cough and cold medicines that were being sold for infants and children under 2 years of age.

The FDA also stated (see <<http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm051137.html>>) that it was reviewing the safety of OTC cough and cold medicines in children aged 2-11. In the meantime it has reiterated advice for parents and caregivers on improving the safety of use of medicines for the treatment of children and has advised them to choose OTC cough and cold medicines with child-proof safety caps, where available, and to store the medicines out of reach of children.

In October 2008 the US CHPA announced (see <[http://www.chpa-info.org/10\\_07\\_08\\_pedcc.aspx](http://www.chpa-info.org/10_07_08_pedcc.aspx)>) that its members were voluntarily modifying the product labels for consumers of OTC cough and cold medicines to state "do not use" in children under 4 years of age. Additionally, the manufacturers stated that they were introducing new child-resistant packaging and new measuring devices for use with the products. The CHPA also announced that manufacturers, in consultation with the FDA, were conducting studies to reaffirm the effectiveness of OTC paediatric cough and cold medicines.

The FDA followed with a public statement (see <<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116964.htm>>) supporting the CHPA's decision and actions restrict the use of these medicines to children 4 years and older.

Note: On 5 May 2009 the CHPA briefed the TGA on its plans for pharmacokinetic and efficacy studies designed to confirm or refine paediatric dosage and to support efficacy and safety. The 8 drugs to be studied represent about 95% of the US paediatric market for cough and cold medicines. The studies will take a number of years to complete and assess.



#### **d. The MHRA**

The MHRA, in consultation with its advisory committees the Paediatric Medicines Expert Advisory Group (PMEAG) and the Commission on Human Medicines (CHM), has reviewed available data on cough and cold medicines available from the published medical literature, information provided by sponsors of such products, and available data on adverse drug reaction reports. It has also taken into account the findings of similar reviews carried out by the TPD and the FDA.

In March 2008 (see <<http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON014446>>, with an update issued in April 2009) the MHRA issued a public statement in several forms that a long list of cough and cold medicines containing one or more of certain antihistamines, antitussives, expectorants and decongestants indicated for children under 2 years would no longer be permitted to be marketed for that age group and that the industry had voluntarily agreed to revise the labelling to remove dosage instructions for children under 2 years of age and to include additional information and advice about use of cough and cold medicines in children aged 2-6 years.

The MHRA advised parents and caregivers that, instead,

*“children suffering from a cough or cold should be treated with paracetamol or ibuprofen to lower the child’s temperature and if they have a cough to use a simple cough syrup (such as glycerol, honey or lemon). For young babies who are having difficulty feeding, nasal saline drops are recommended to help thin and clear nasal secretions. Vapour rubs and inhalant decongestants, which can be applied to a child’s clothing, can also be used to provide relief from a stuffy nose.”*

The statement also noted that in the UK there had been 5 deaths but that overall there had not been as serious a problem with adverse events in children under 2 years as had been experienced in the USA.

*“In the UK there have been far fewer reports, but the data does suggest that children under 2 are at greater risk of any potential harm. This is because children under 2 are more vulnerable due to their small size and therefore may be particularly susceptible to the effects of overdose. This new advice will reduce that possibility and is a precautionary measure.”*

The April press release stated that the CHM had

*“noted a lack of robust evidence for the efficacy of these medicines in children and that medication does not affect the course of the illness: it can only provide, at best, symptomatic relief.”*

Further, the PMEAG and the CHM had

*“concluded, on the basis of available evidence, that the balance of risks and benefits associated with the use of cough and cold medicines for children younger than 2 years is no longer favourable. Furthermore, the Commission advised that medicines in this therapeutic range that are suitable for children aged 2-6 years should contain updated information.”*

In February 2009 the MHRA issued a further statement (see <<http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON038902>>) advising that their reviews of the safety and efficacy data for cough and cold medicines and the benefits and risks of these products had led to a decision on the advice of the CHM that these medicines should not be used for children under 6 years of age and should not be recommended for children aged 6-12 years. The MHRA has also determined that all liquid OTC cough and cold medicines containing the ingredients it has reviewed must be in child resistant containers.

In February 2009 the MHRA also made changes to the classification in the UK of some of the drug substances used in cough and cold medicines. Currently, most active ingredients in such medicines are classified as “pharmacy medicines”, but guaifenesin, ipecacuanha, oxymetazoline, phenylephrine and xylometazoline, senega and ammonia are currently “general sales” medicines. As from March 2010 all of these substances other than senega and ammonia will become “pharmacy medicines” if they are presented for use in children under 12 years of age. The UK classifications will then be the same as those applying in Australia as far as products for use in children under 12 years of age is concerned.

The TGA has obtained from the MHRA **confidential** copies of the Overview and detailed report of the MHRA’s review of the literature and other relevant information that led to its conclusions and recommendations above. These MHRA documents are confidential to the TGA and may only be viewed by TGA personnel.

### **e. Medsafe**

Many of the cough and cold medicines available in Australia are also likely to be marketed by the same (or related) sponsors in New Zealand. The scheduling (classification) and labelling of products in the two countries has been largely harmonised and, consequently, regulatory decisions made in Australia or New Zealand may affect the other country to some extent.

At its June 2006 meeting the New Zealand Medicines Classification Committee (MCC) discussed the safety of antihistamines for use in the treatment of infants and recommended that sedating antihistamines should be classified as prescription medicines when indicated either singly or in combination for use in children under two years of age. The Committee also recommended that the Australian NDPSC should be asked to harmonise on this recommendation. The Committee had earlier expressed concern that sedating antihistamines were available over the counter for children under two years of age. Some sedating antihistamines had been implicated in sudden death in this age group. There was also anecdotal and published evidence of misuse and abuse of these medicines in children. The Committee was unanimously of the view that sedating antihistamines should be used in this age group only under medical supervision. The Committee also agreed that the NDPSC should be asked to harmonise on this recommendation.

At its December 2007 meeting the MCC again considered the safety and efficacy of sedating antihistamines and recommended that Medsafe review the labelling of all sedating antihistamine products to ensure that these were contraindicated in children under two years of age and that there was a warning statement about use with other cough and cold medicines, that Medsafe inform doctors about the use of sedating antihistamines and other cough and cold preparations in children under two years of age, and that future applications for consent to market sedating antihistamines and cough and cold products for children should be based on safety data obtained from proper studies conducted on children in the relevant age group.

In January 2008 Medsafe issued a media statement (see <<http://www.moh.govt.nz/moh.nsf/indexmh/children-under-two-should-not-be-given-cough-and-cold-medicines?Open>>) that the NZ Medicines Adverse Reactions Committee (MARC) had reviewed the safety and effectiveness of cough and cold medicines when used in children and, as a result, Medsafe was issuing a warning that “Cough and cold medicines should never be given to children aged less than two years of age and when given to older children extra care should be taken.”

In March 2009 Medsafe issued a statement (see <<http://www.moh.govt.nz/moh.nsf/indexmh/childrens-use-of-cough-and-cold-medicines-reviewed?Open>>) that, by 1 May 2009, it expected all cough and cold medicines marketed in New Zealand to have on their labels the statement “Must not be used in children under two years of age”, or words to that effect. As from that date all affected products in pharmacies have been required to carry that statement



either on the printed label or, in the case of older stock, on a sticker attached to the label by the sponsor or the pharmacist.

Medsafe also stated that, following the decisions of the Canadian and United Kingdom regulatory authorities to advise against the use of cough and cold medicines in children under 6 years of age, Medsafe would be seeking further information from those agencies and would, if appropriate, reconsider its earlier decisions regarding the age under which these medicines should not be used.

In late September 2009 Medsafe notified New Zealand sponsors that it had determined that:

1. cough and cold medicines should not be used in children under 6 years of age
2. the labelling and any product information documentation for these products must be amended to include:
  - a warning that the medicine is not to be used in children aged under 6 years of age (and any dosage instructions for such children must be removed from the label)
  - a maximum daily dose
  - advice to parents and guardians to seek advice from a healthcare professional before using the medicine in children aged 6 years and older
  - where applicable, a warning about sedation as a side effect
  - a warning that the medicine should not be taken with any other medicine (including complementary medicines) to treat the symptoms of the common cold
3. these products must be supplied in child-resistant packaging
4. accurate measuring devices must be supplied with these medicines
5. Consumer Medicine Information must be prepared for publication on Medsafe's web site.

Medsafe expects these changes to be complete by the 2011 cough and cold season.