Public Consultation on Proposed Amendments to the Poisons Standard (codeine)

Notice under subsections 42ZCZL of the Therapeutic Goods Regulations 1990 (the Regulations)

The delegate of the Secretary to the Department of Health publishes herein all valid public submissions made in response to the invitation for public submissions on the proposed amendments to the Poisons Standard. In order to give due consideration to the submissions received in the interim decision public consultation period and to seek further advice from the Advisory Committee on Medicines Scheduling (ACMS) at its March 2016 meeting, the medicines scheduling delegate on 18 November 2015 deferred a final decision on the proposed codeine re-scheduling. The TGA then sought further advice and public comment on several options for codeine re-scheduling via an additional consultation period that was open from 10 December 2015 through 29 January 2016. These submissions were considered by the medicines scheduling delegate when making their final decision.

In accordance with the requirements of subsection 42ZCZL of the Regulations these submissions have had their confidential information removed.

Materials claimed to be commercial-in-confidence were considered against the guidelines for the use and release of confidential information set out in Chapter 6 of the Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015), issued by the Australian Health Ministers' Advisory Council. The SPF is accessible at https://www.tga.gov.au/publication/ahmac-scheduling-policy-framework-medicines-and-chemicals.

are no longer bothersome, at which point they cease taking the product. Analgesic use is different with some users inappropriately continuing use for the treatment of chronic pain. Due to the differences in the way these different products in different categories are used, their associated risks should be considered independently of each other.

Concern expressed about the potential for demand for OTC analgesics with codeine to transfer to cold and flu products with codeine, has been allayed. Historical evidence strongly supports there is no transfer of demand. This applies to both S3 pseudoephedrine and S2 phenylephrine-codeine combinations

The unintended consequences of scheduling changes to cold and flu products with codeine are likely to have negative economic impacts to the patient and the health system, placing undue pressure on the GP with extra patient load and potential for inappropriate antibiotic prescribing as well as an increased PSE load in pharmacies and the supply chain which increases the risk of illicit activity associated with PSE.

As with all drugs and chemical substances, [redacted] acknowledges the risk of misuse or addiction. However, no matter what medicine we are discussing, these risks have always been taken into context against the greater good. That is the hallmark of our industry. We need only review the facts to determine whether the greater good is what is being considered in this proposal. Given the rate of addiction and the rate of adverse events (including death) that occur every year related to codeine-use *VERSUS* the rate of addiction and adverse events related to more pernicious drugs like alcohol and tobacco which are sold in uncontrolled environments and without oversight from a qualified HCP, is making wholesale changes to the scheduling of codeine a reasonable and appropriate focus?

We know the vast majority of consumers accessing codeine-containing medicines use these products properly and, in purchasing them, have the opportunity to interact with a credentialed healthcare provider in community pharmacy. Rescheduling these medicines will not solve the complex problem of addiction – it will merely shift it to another healthcare setting and, bring with it a host of unintended consequences which, the former NDPSC acknowledged, are most certainly not in the public interest.

[redacted]

[redacted]

Appendix 2
[redacted] submission in the Delegate's Interim decision on Codeine
October 2015

[redacted]

[redacted]

Thursday 15th October 2015

Medicines Scheduling Secretariat
Therapeutic Goods Administration
136 Narrabundah Lane
Symonston ACT 2606
Australia

Dear Sir/Madam,

Re: Public Submission – under Reg. 42ZCZK of the Therapeutic Goods Regulations 1990. ACMS #15

Submission on the Delegate's interim decision to delete the current Schedule 2 and 3 entries for codeine and amend the current Schedule 4 and 8 entries to reflect these changes

[redacted] is extremely disappointed with, and strongly opposes the Delegate's interim decision to up-schedule codeine containing cold and flu medicines from Schedule 2 and Schedule 3 to Schedule 4 for the following reasons:

1. There was a lack of detail with the initial proposed scheduling agenda item for codeine to allow interested parties to make considered and adequate submissions as required by clause 42ZCZP of the Therapeutic Goods Regulations (the **Regulations**).
2. The risk/benefit profile of codeine containing cold and flu preparations has not changed since the NDPSC decision in 2009 which deemed Schedule 2 and Schedule 3 as appropriate. This decision was affirmed by a Delegate in September 2011 where scheduling of codeine was considered as part of the cold and cough preparation review and, on the recommendations of the Advisory Committee on Medicines Scheduling **(ACMS),** the Delegate decided there should be no change to the scheduling of codeine in cold and cough preparations.
3. There has been no increased demand or change in patterns of use of codeine containing cold and flu products since the up-scheduling of codeine containing analgesics in 2010. Any concern that may have been held in relation to transference of abuse or dependency from analgesics has been addressed in the [redacted] submission of 7th May 2015.
4. There is no evidence of harm, abuse or dependency associated with codeine containing cold and flu preparations.
5. There has been no effort made to distinguish the risk/benefit profile of codeine containing analgesics to that of codeine containing cold and flu preparations. The majority of the reasons related to codeine containing analgesics. Distinguishing the risk/benefit profile of codeine containing products in different categories should have been a critical consideration. Section 52E(1)(b) of the Therapeutic Goods Act (the **Act**) provides that the Delegate must consider the purpose for which a substance is to be used and the extent of use of the substance.

6. Evidence upon which the Delegate has relied upon, such as, but not limited to *The National Opioid Pharmacotherapy Statistics in 2013*, relates to codeine containing analgesics, not codeine containing cold and flu preparations, and is therefore not relevant.
7. High risk populations that are at risk of morphine overdose due to genetic differences in the expression of the CYP2D6 enzyme (ultra-rapid metabolisers) include children under 12 and breastfeeding mothers. These populations can be contraindicated for codeine containing cold and flu products (codeine containing [redacted] already excludes these populations from use).
8. There are no safety issues raised that cannot be overcome through adequate labelling warnings, contraindications and further education. This is a strategy that has successfully been adopted by other regulatory agencies of similar standard. The opinion of the Delegate that labelling is not sufficient is incorrect.
9. Finally, and in any event, the proposed effective date is unrealistic and in the height of the cold and flu season. The timing will not give sponsors of cold and flu products (which are seasonal), enough time to exhaust their products which they would have already committed to by the date of the Delegate's final decision due to complex supply chains and long production lead times.

Executive Summary:

Based on the reasons for the interim decision on the proposal to up-schedule codeine containing cold and flu preparations, it is clear that the decision has not been evidence based. The reasons for the decision demonstrate that there is no evidence relating to an increase in harm, abuse or dependency specifically relating to codeine containing cold and flu preparations. In fact, there is limited reference (at best) to the evidence provided by [redacted] for the 15th meeting of the ACMS.

The proposed agenda item for codeine published on the TGA website on the 2nd April 2015 did not provide sufficient detail of the proposed amendment, to inform the public so that adequate submissions and proper critiquing of the evidence could be made in accordance with the statutory requirements. The agenda's reference to Schedule 2 codeine was insufficient to be considered an effective consultation process. There was no precise intent. In the submission dated 7th May 2015, [redacted] along with a number of other interested parties, including but not limited to [redacted] [redacted] and [redacted], highlighted the concerns about the lack of evidence or rationale behind the proposal. There is little to indicate that the evidence that was considered by the ACMS and Delegate specifically related to codeine containing cold and flu preparations.

[redacted] requested that in the interest of procedural fairness, any evidence submitted in support of the proposed scheduling changes, specifically for codeine containing cold and flu preparations be made publicly available and that any decision relating to the up-scheduling of codeine be deferred until the evidence can be assessed by parties with an interest in codeine. Again, [redacted] would like to express disappointment that this request appears not to have been considered. The interim decision has been made with very little consideration of the compelling evidence that there has been no abuse or dependency of codeine containing cold and flu products. There has been no change in the risk/benefit profile since the NDPSC decision was made in 2009 to up-schedule codeine containing analgesics but

maintain the S2 entry for cold and flu preparations. In fact, the interim decision did very little to distinguish between codeine containing analgesics and codeine containing cold and flu products which is a key consideration.

Given the lack of robust and credible evidence to support the up-scheduling of codeine containing cold and flu products we request the publication of the methodology adopted to conclude that the risk/benefit profile (that was deemed appropriate by the NDPSC in 2009 for codeine cold and flu preparations), has shifted to warrant a drastic scheduling change, and not be overcome through other feasible means such as label restrictions. [redacted] trusts that for a decision of such magnitude and with such a profound impact to consumers and the public health system in Australia, a robust and validated model, such as the value-tree framework approach developed by Brass *et al*[1], which is used by other regulators with similar regulatory standards like the MHRA, would have been used.

[redacted] would like to restate that cold and flu preparations containing codeine should be excluded from any consideration of measures aimed at addressing concerns that are associated with analgesic codeine combinations. No evidence of inappropriate use of cold and flu preparations containing codeine has been identified since the NDPSC decision in 2009 to up schedule codeine containing analgesics. The concerns that the problem of abuse/misuse may have shifted to cold and flu preparations that contain codeine have been dispelled with the data on seasonal sales submitted by [redacted] on the 7th May 2015, and are also negated by the lack of evidence of abuse in this category (also reflected in Adverse Events data).

[redacted] hereby formally requests that the Delegate reconsiders the interim decision in relation to the scheduling of codeine for cold and flu preparations. The current scheduling remains appropriate and there should be no change to the schedule 2.

Procedural and Administrative Errors relating to the interim decision:

[redacted] would like to draw your attention to Therapeutic Goods Regulation clause 42ZCZK which states that a notice must set out the details of the proposed amendment. The notice published on 2nd April 2015 did not satisfy this requirement, particularly in respect of the amendment to Schedule 2. It was not clear whether any particular change or any deletion was proposed, as it did not set out the details of the proposed amendments properly. The interim decision is to completely delete all S2 and S3 entries for codeine. There has been a failure in the process as the call for public comment did not provide sufficient opportunity for the public to respond as contemplated by the legislation.

[redacted] would also like to draw your attention to subsection c, of clause 42ZCZP of the regulations, it states:

[1] Brass EP, Lofstedt R, Renn O. Improving the Decision-Making Process for Nonprescription Drugs: A Framework for Benefit-Risk Assessment. Clin Pharmacol Ther 2011;90:791-803

*Inviting persons who made a submission in response to the original invitation under paragraph 42ZCZK(1)(d) to make further submissions to the Secretary in relation to the interim decision within 10 business days after publication of the notice (the **second closing date**);*

The publication of the interim decision occurred on the 1st of October 2015. The second closing date (as referenced above) has been stated to be 15th October. Due to the public holiday in the ACT & NSW on Monday 5th October 2015, the second closing date of the 15th of October is only 9 business days, not the 10 business days as stated in the **Regulations.**

Additionally, the public submissions for the Advisory Committee on Chemical Scheduling **(ACCS)** and the joint ACCS/ACMS meeting were made available through the TGA website on the 1st of October 2015, however the public submissions received for the ACMS meeting were not made available through the TGA website until after the close of business on Tuesday 6th October, thereby reducing the time by which sponsors and or interested parties have to review the data submitted and respond by the 15th October, again impacting the adequacy of submissions given the limited review period.

[redacted] would also like to highlight an administrative error made by the TGA. During the initial public submission stage, [redacted] provided a full version of the submission for the ACMS and Delegate to evaluate. A redacted version of the submission was provided to be used for publication on the TGA website. We can only express our disappointment again when it became apparent that the full [redacted] submission was placed on the TGA website, rather than the redacted version provided on the 7th May 2015. It is acknowledged by [redacted] that this was corrected quickly upon advising TGA of this error. Despite TGA acting quickly on the request, and we thank the TGA for that action, elements of the confidential sections of the [redacted] submission were reported in the media.

Considerations under section 52E of the Therapeutic Goods Act 1989

All the matters in section 52E(1) of the Act which must be considered by the Delegate in making a decision have been considered as part of this submission. The position in respect of each consideration in s52E(1) of the Act remains unchanged since the NDPSC 2009 decision that deemed Schedule 2 appropriate for codeine containing cold and flu preparations. We comment on certain of these matters further in response to specific comments later in this submission.

S52E(1)(a) *"the risks and benefits of the use of a substance"*

Since the NDPSC decision in 2009, [redacted] has been proactively monitoring the supply of codeine containing cold and flu preparations, as well as adverse events reporting. No evidence has emerged to suggest that the risk-benefit/abuse/misuse profiles have changed since this decision was made in 2009.

In fact on review of the reasons for the TGA Delegate's interim decision, the reasons are heavily weighted towards codeine containing analgesics, and very little has been done to distinguish these products from codeine containing cold and flu products. This decision is therefore not evidence based with respect to cold and flu products.

The Delegate has highlighted the risk of medication misadventure and deliberate misuse with the relative lack of efficacy compared with safer products. In the absence of compelling evidence to suggest that the risk/benefit profile of codeine containing cold and flu preparations has changed since the NDPSC decision in 2009, we maintain that the current scheduling for cold and flu products remains appropriate.

Furthermore it is important to note that while historically codeine containing cold and flu products have been referred to as codeine containing cough and cold products, in fact "cough" is not a TGA approved indication for codeine containing [redacted] The only evidence of efficacy in relation to cold and flu products cited by the Delegate related to use for cough. The Delegate did not refer to any evidence of lack of efficacy of containing cold and flu products.

S52E(1)(b) ***"the purposes for which a substance is to be used and the extent of use of a substance"***
Codeine containing [redacted] products have been responsibly and safely used by millions of Australians since at least [redacted] to treat their self-limiting cold and flu symptoms. Cold and flu symptoms are short term and the products are typically limited to three day use and by virtue of their indications they are not used chronically. All codeine containing products are indicated for adults and children 12 years and over, therefore any reasons for the Delegate's decision relating to children under 12 years of age are not applicable to [redacted] products impacted by this decision. Furthermore, the Delegate can propose an alternate option to scheduling by contraindicating for this age group.

S52E (1)(c) ***"the toxicity of a substance"***
As with other opioid analgesics, codeine is potentially capable of causing respiratory depression and reduced levels of consciousness in overdose. While such concerns in relation to toxicity must be considered, the low dosage of codeine and the combination of other substances in cold and flu preparations significantly reduce the risk or likelihood of overdosing on codeine through cold and flu preparations.

Furthermore, the majority of risk of harm from toxicity comes from the ibuprofen and paracetamol (hepatic injury, gastrointestinal perforations and hypokalaemia) which are combined with the codeine. This is a concern relating to codeine containing analgesics given these products are used for pain management and the potential for chronic use of these products.

Lastly, the Delegate's decision has focused on toxicity of codeine as it affects ultra-metabolisers, due to its transformation into morphine, which may cause respiratory depression and possible death. As indicated later in our response, ultra-metabolisers are an identified group, and the potential harm to this "at risk" group can be managed through effective labelling by ensuring these groups are contraindicated. Furthermore, in considering the weight given to this risk affecting a minority in the Delegate's decision, we note that the Advisory Committee on the Safety Of Medicines **(ACSOM)** was "undecided" in its meeting statement No 28 from 10 July 2015 whether the risks associated with ultra-rapid metabolism of codeine outweigh the benefits of codeine for any indication in ultra-rapid

metabolisers of any age. The meeting statement further notes that adults will generally know how well codeine works for them and have the capacity to self-regulate by adjustments to the dosage regimen.

S52E(1)(d) ***"the dosage, formulation, labelling, packaging and presentation of a substance"***
Codeine containing [redacted] products contain less codeine per dosage unit than codeine containing analgesics. Furthermore, these products contain multiple active ingredients (including Paracetamol and Phenylephrine) making the potential for abuse or misuse even lower, which was highlighted and recognised by the NDPSC in 2009. The packaging and presentation are in line with the Australian requirements as set out in Therapeutic Goods Order 69, ARGOM and RASML/MASS 2014. [redacted] has included additional safety information not required by legislation. Despite RASML not requiring a warning regarding addiction, [redacted] includes a statement that codeine can be addictive in accordance with New Zealand's Medsafe requirements. [redacted] also contraindicates use of codeine containing [redacted] products in children under 12 and, breastfeeding mothers Furthermore, our Company Core Data sheet has recently been updated to reflect the genetic differences in expression of the CYP2D6 enzyme which can result in differences in the extent to which codeine is metabolised, this will be reflected on labelling shortly. Therefore any matters raised in the interim decision relating to these concerns already have been or will shortly be addressed through effective labelling despite there being no such required warnings in Australia to date. Up-scheduling is irrational given measures such as label warnings can adequately address these safety issues.

S52E(1)(e) ***"the potential for abuse of a substance"***
The decision of the NDPSC in 2009 that deemed Schedule 2 appropriate for codeine containing cold and flu preparations was given on the grounds that there was no evidence of abuse in this category. This was likely due to the fact that codeine containing cold and flu preparations include multiple active ingredients, they have lower levels of codeine compared with codeine containing analgesics and cold and flu symptoms are self-limiting and for short duration. All of these components together help reduce the abuse potential, as recognised by the NDPSC in the June 2009 meeting.

There is no current or historical evidence to support the existence or potential of widespread abuse of cold and flu preparations containing codeine. In fact we are not aware of evidence, nor have we seen any evidence reviewed by the ACMS or Delegate, to suggest there has been an increasing amount of harm from codeine containing cold and flu products since the decision was made by the NDPSC in 2009 to exclude cold and flu products containing codeine from any consideration of measures aimed at addressing analgesic codeine combinations in 2009.

On the contrary, the data submitted by [redacted] in its 7th May 2015 submission, together with the [redacted] Adverse Events reporting, provides evidence supporting the fact that abuse has not shifted to codeine containing cold and flu preparations since codeine containing analgesics were up-scheduled in 2009. This data dispels any concerns that up-scheduling codeine containing analgesics only would shift abuse to codeine containing cold and flu preparations, and demonstrates that there is no evidence of abuse. On this basis, the Delegate has failed to provide any evidence to support the potential for abuse

as it specifically applies to codeine containing cold and flu products and has failed to consider the relevant evidence provided in the [redacted] submissions of 7th May 2015 which addresses this.

S52E(1)(f) *"any other matters that the Secretary considers necessary to protect public health"* and other relevant matters

Cold and flu medicines containing codeine are responsibly used by millions of Australians appropriately opting for self-care for what are short-term, episodic and self-limiting conditions. The appropriate care setting for these treatments to be administered is community pharmacy. Millions of Australian consumers rely on their codeine containing cold and flu preparations to get them through their cold and flu and they are used responsibly as there is no evidence to suggest otherwise. The unintended consequences of scheduling changes to codeine containing cold and flu products are likely include negative economic impacts to the patient and the health system, placing undue and unnecessary pressure on the GP with extra patient load (and incremental cost to the public health system) and potential for inappropriate antibiotic prescribing as well as an increased pseudoephedrine load in pharmacies and the supply chain which increases the risk of illicit activity associated with Pseudoephedrine.

Given there has been no evidence of abuse in this category, and no new risks have been raised by the Delegate that cannot be overcome through sufficient label warnings, there is no rational basis for changing the current scheduling of codeine containing cold and flu products.

Responses to specific reasons for the Delegate's decision

For ease, [redacted] has listed out each of the reasons for the Delegate's interim decision which highlight that the weighting of the reasons are to codeine containing analgesics, not codeine containing cold and flu products. Furthermore, for any reason that is not specifically related to codeine containing analgesics there is no reason as to why that cannot be addressed through other means, such as labelling restrictions/education (especially prescribers), as detailed below.

Delegate's Comment:
Risks of medication misadventure through polymorphic metabolism, deliberate misuse/abuse combined with the relative lack of efficacy compared to safer products.

[redacted] Response:

In the absence of compelling evidence to suggest that the risk profile of codeine containing cold and flu products has changed since the NDPSC decision in 2009, [redacted] maintains that the current Schedule 2 entry remains appropriate.

The concerns around polymorphic metabolism have been a known risk for a number of years. There is no evidence, based on adverse event reporting, of medication misadventure through polymorphic metabolism for [redacted] codeine-containing cold and flu products. Notwithstanding that there is no such evidence, [redacted] is addressing this risk through company-initiated new labelling regarding genetic differences in the way that codeine is metabolised. Such labelling changes have been considered adequate by other regulators such as Medsafe and MHRA We comment further on polymorphic metabolism later in this submission.

Since the last review of scheduling in 2009, there is no new evidence demonstrating that codeine containing cold and flu products are being misused and/or abused. Consequently, the risk/benefit profile that was deemed appropriate by the NDPSC for codeine containing cold and flu products in 2009 remains unchanged.

The [redacted] submission of 7th May 2015 adequately addressed this issue as supported by:

- The 2009 NDPSC decisions
- Company Adverse Events reporting from 2010 - 2015
- IMS and AZTEC sales data monitoring supply and trends of OTC codeine containing products

This data demonstrated that sales of codeine containing cold and flu products follow seasonality shifts, the same sales trends as non-codeine containing cold and flu products. If codeine containing cold and flu products were subject to abuse and/or misuse there would be no seasonality in demand displayed, and sales data would trend differently to the non-codeine containing cold and flu products.

In the June 2009 meeting of the NDPSC, the Codeine Working Party (CWP) state that *"the TGA had not evaluated efficacy data for any OTC product containing codeine. While efficacy data were critical to an assessment of overall risk-benefit efficacy per se was not a primary issue for consideration under section 52E….."* Since that time there has been no change in the efficacy, since that time no change to the risk, therefore the risk/benefit profile remains unchanged for codeine containing cold and flu preparations.

Delegate's Comment:
The risk/benefit profile for codeine in doses of 8 mg – 15 mg per dosing unit in combination with other analgesics is unfavourable. There is also a lack of evidence of any benefit of codeine over placebo in the relief of cough, making the risk/benefit profile for this indication unfavourable also. Codeine demonstrates marked variability in its transformation to morphine in different individuals, with the potential for very severe toxicity in ultra-rapid metabolisers.

[redacted] Response:
Again, in the absence of new evidence suggesting that codeine containing cold and flu products are being deliberately misused and abused, or that there has been an increase in adverse events associated

with codeine in cold and flu products, since the 2009 NDPSC decision, the risk/benefit profile for this specific category of products remains unchanged.

The lack of evidence that the Delegate cites of benefit of codeine over placebo for cough is not applicable to codeine-containing cold and flu products. Codeine is not indicated for the relief of cough in cold and flu products. **Any decision or recommendations based on a lack of benefit when comparing the anti-tussive activities of codeine against placebo in cold and flu products are invalid due to the fact that these products are not indicated for the relief of cough**.

The Delegate has not cited evidence of lack of efficacy of codeine containing analgesics in the above comment. As mentioned above, millions of Australians choose codeine containing cold and flu products for treatment of their cold and flu symptoms.

Further, there is no evidence to suggest that the use of codeine containing cold and flu products has been linked to cases of respiratory depression or death due to use by ultra-rapid metabolisers.

It is important to highlight that while the issue with polymorphic metabolisers is serious (and is taken seriously by [redacted] the main groups at risk have been identified to be children under 12 years, children under 18 years if they have had post-operative codeine analgesia following surgery for tonsillectomy or adenoidectomy and breastfeeding mothers.

From a [redacted] perspective, children under 12 years are not at risk in relation to codeine containing [redacted] as these products are contraindicated for children under 12 years. Furthermore, all reports of toxicity in this age group have been in relation to codeine containing analgesics given to children to manage pain after tonsillectomy and/or adenoidectomy. The likelihood that codeine containing cold and flu products would be used in this context is extremely unlikely.

Any concerns with the "at risk groups" can be managed through effective labelling with clear warnings and contraindications, as is the case with all [redacted] products that contain codeine.

The approach to up-schedule all codeine containing products to mitigate the risk associated with this population is unjustified and unnecessary and not likely to be overcome if a patient was to visit a GP versus a Pharmacy/Pharmacist.

In many countries where the regulators have regulatory standards similar to those of the TGA (including the USA, UK and New Zealand) they have taken the prudent regulatory approach by contraindicating the use of codeine in children under 12 and breastfeeding mothers due to issues relating to the genetic differences in the expression of the CYP2D6 enzyme, yet certain of these product are still available OTC (including the USA, which is contrary to the media statement published by the TGA in relation to the proposed up-scheduling of codeine on 1st October 2015). These actions were taken as early as 2012 and 2013. The TGA has not undertaken any such regulatory action.

Medsafe and the Medicines Adverse Reactions Committee in New Zealand (MARC) recently reviewed the use of codeine containing cough and cold medicines and they concluded that there was not enough evidence to support the use of these medicines in younger children. As a result, the decision was made to contraindicate the use of codeine in children under 12 years, which further confirms the risk/benefit profile is only a significant issue for younger children and breast feeding mothers (Medsafe have required a warning for breastfeeding mothers since 2010). This also aligns with the conclusions of the Advisory Committee on the Safety of Medicines (**ACOSM**) whereby they concluded that the risks of respiratory depression and possible death in the context of ultra-rapid metabolism associated with codeine outweigh the benefits of codeine for all indications in children under the age of 12 years and that the risks to breastfed infants associated with ultra-rapid metabolism of codeine by their mothers outweigh the benefits of codeine for any indication by breastfeeding mothers. However the ACSOM was **undecided** whether the risks associated with ultra-rapid metabolism of codeine outweigh the benefits of codeine for any indication in ultra-rapid metabolisers of any age. Furthermore, the interim decision assumes that this population would be identified during the course of a prescription being issued. There is no evidence that this is currently occurring with prescription codeine therefore up-scheduling codeine for this reason would appear to serve no purpose.

Until such time that there is solid evidence to support this notion, then sufficient label warnings to highlight the risk to certain populations most at risk is an appropriate measure and [redacted] welcomes such changes.

The TGA have had the opportunity to consult on any appropriate RASML/MASS changes in respect of ultra-rapid metabolisers, yet to date this has not occurred.

Delegate's Comment:
OTC intended for management of acute self-limiting pain, however, there is inappropriate use for chronic pain.

[redacted] Response:
This is not applicable and irrelevant in the context of codeine containing cold and flu products. This reason specifically relates to codeine containing analgesics, which have always been differentiated from codeine containing cold and flu products. The NDPSC have acknowledged in October 2009 that "*unlike pain, cold and flu were self-limiting in duration and there were no reports that use of CCCC was currently leading to misuse or abuse*" and they agreed that *"these products had multiple therapeutically active ingredients and this may diminish abuse/misuse potential…."*. The patterns of use of cold and flu products have not changed since this time.

Delegate's Comment:
Purpose is questioned since benefit is low.

[redacted] Response:
As above, in the absence of new and compelling evidence to suggest that the risk/benefit profile has changed since the NDPSC decision in 2009 specifically for codeine containing cold and flu preparations then this reason is not applicable to codeine containing cold and flu products since the Delegate needs to review this in the context of risk/benefit profile.

It is assumed based on the other comments made by the Delegate that the benefit referred to above relates to the efficacy of codeine. The codeine containing [redacted] products are all multi-active products to treat the symptoms of cold and flu. [redacted] would like to advise that there are Cochrane reviews of paracetamol plus codeine[2] that have established that this combination is efficacious

Further, these products are available for self-selection by consumers. If consumers did not believe that the codeine-containing [redacted] products were efficacious (the benefit) then repeat purchase would never occur, irrespective of what marketing or retail campaigns are put in place. [redacted] is Australia's #1 cold and flu brand. Being the #1 brand does not occur with non-efficacious products. We therefore question the perception of the Delegate that the benefit connected with this purpose is low.

Delegate's Comment:
The purposes for which codeine is intended to be used are for Schedule 2 products for the "treatment of coughs and colds" and for Schedule 3 products for the "temporary relief of strong pain and discomfort associated with a number of different medical conditions."

[redacted] Response:
There are a number of Schedule 3 cold and flu products that contain codeine in combination with pseudoephedrine. This comment by the Delegate gives no regard to these products.

[redacted] Cold and Flu products containing 9.5 mg codeine phosphate, have been used responsibility by millions of Australians on an annual basis. When considering the large selection of cold and flu medication available as both Over the Counter (**OTC**) and general sale, it is apparent that these products serve a purpose and provide a benefit in the treatment of cold and flu symptoms.

As cited above, in the absence of new, credible and robust evidence to suggest that the risk/benefit profile has changed since the NDPSC decision in 2009 specifically for codeine containing cold and flu preparations (not cough) the current scheduling arrangements for cold and flu preparations remains

[2] Toms L, Derry S, Moore RA, McQuay HJ. Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. *Cochrane Database Syst Rev* 2009;(1):CD001547.

totally appropriate. As highlighted above, “cough” is not an approved indication for codeine containing [redacted] products.

Delegate’s Comment:
Codeine shares the properties of other opioid analgesics and is potentially capable of producing dependence and, in overdose, respiratory depression and reduced level of consciousness.

[redacted] Response:
It is important to recognise that codeine has some addictive potential. This is not new.

However, there is no evidence to suggest that codeine containing cold and flu preparations are being abused. In the June 2009 NDPSC meeting, the committee agreed that codeine containing cold and flu products had multiple therapeutically active ingredients and these together might diminish the abuse/misuse potential of these preparations; in addition, they have a lower amount of codeine per tablet compared with codeine containing analgesics. These present a lower risk profile for dependence, abuse and adverse effects.

Medsafe, the MHRA and certain other similar jurisdictions have required mandatory labelling changes to highlight that codeine has addictive potential and use should be contraindicated for children under 12 years and breast feeding mothers due to ultra-rapid metabolisers. **This applies to codeine-containing products, which in some cases are available OTC in those countries.** The TGA has not mandated such warning statements.

[redacted] takes the safety of our consumers very seriously, and while not a legislated requirement in Australia, [redacted] is in the process of including warning statements relating to high risk populations on all codeine containing products. As mentioned above, [redacted] includes a warning statement regarding addictive potential of codeine.

It is also important to note that all OTC products need to be taken in accordance with the label directions. Many well established and safe non-prescription medicines can cause significant harm if medicine misadventure occurs. It is illogical to single out codeine, particularly in cold and flu products, to justify up-scheduling based on harm in an overdose situation.

Again we reiterate that there is no evidence to support codeine containing cold and flu products are being abused and/or leading to respiratory depression and reduced level of consciousness, assumingly if taken by ultra-rapid metabolisers.

Delegate's Comment:

Codeine, as a prodrug, causes its direct toxicity primarily through its biotransformation into morphine. The metabolic polymorphism discussed above leads to major variability within the population in terms of the extent and rapidity of this conversion to morphine. Ultra-rapid metabolisers, who have an accelerated rate and higher extent of conversion, are exposed to morphine concentrations that are many-fold higher than those reached in poor metabolisers. This variant is found in up to 10% of Caucasians, and higher proportions of populations of North African, Oceanic and Middle Eastern origin. Very few individuals are aware of their own metaboliser status, and it would thus be very difficult to protect ultra-rapid metabolisers by way of warnings. High concentrations of morphine in the plasma can lead to serious sedation and respiratory depression, and potentially to death.

[redacted] **Response:**

As stated above this reason is not aligned with the ACSOM. This group of experts remained undecided on whether the risks associated with ultra-rapid metabolism of codeine outweigh the benefits of codeine for any indication in ultra-rapid metabolisers **of any age**.

The main 'at risk' groups include children under 12 years, children under 18 years following post-operative analgesia and breastfeeding mothers.

The main conclusions of the review aligned with views from Medsafe, FDA and the MHRA (all of which still allow codeine to be available OTC in certain products). The conclusions were:

- That the risks of respiratory depression and possible death in the context of ultra-rapid metabolism associated with codeine outweigh the benefits of codeine for all indications in children under the age of 12 years.
- The risks to breastfed infants associated with ultra-rapid metabolism of codeine by their mothers outweigh the benefits of codeine for any indication by breastfeeding mothers

However ACSOM was **undecided** whether the risks associated with ultra-rapid metabolism of codeine outweigh the benefits of codeine for any indication in ultra-rapid metabolisers of any age.

This is supported by the fact that there have been no reported issues of codeine toxicity due to serious sedation and respiratory depression, and death, with the use of codeine containing [redacted] This further confirms that it is incorrect to conclude that the risk is true for any indication or population of any age group and that labelling restrictions cannot be an appropriate measure to exclude to populations most at risk.

Until such time there is solid evidence to support the risks as highlighted in the Delegate's comments, the current scheduling remains appropriate for cold and flu preparations containing codeine.

Sufficient label warning statements excluding the use of these preparations by the high risk populations is the appropriate measure to mitigate the risks. It is inappropriate to propose such a significant scheduling change as the only way to adequately address the concerns relating to ultra metabolisers, especially when the ACSOM still remain undecided.

Codeine containing [redacted] is not only contraindicated for children under 12 and has a breastfeeding warning on labelling, but it is also not indicated for pure pain management.

Delegate's Comment:
The potential for severe adverse effects at "usual" doses in ultra-rapid metabolisers is such that codeine appears to be an unsuitable candidate for OTC availability, with either S2 or S3 scheduling. This conclusion applies equally well to the products intended for treating coughs and colds, and those intended for the treatment of pain

[redacted] Response:
The greatest risk of severe adverse reaction and toxicity are to children and breast feeding mothers. Therefore, by contraindicating its use for these populations, mitigates risks associated with ultra-rapid metabolisers. Based on this logic, many OTC active ingredients would not be able to be considered a suitable candidate for OTC availability if there are associated contraindications for certain populations. Furthermore, [redacted] has not received any reports of respiratory depression in any population (low or high risk) associated with the codeine containing products which are supplied by [redacted]

The "usual" doses of codeine in cold and flu products are less than the levels of codeine in primary combination analgesics. It is difficult to understand how a conclusion can be drawn that applies equally to analgesics and cold and flu products. This is scientifically illogical.

The conclusions of the review by the ACSOM aligned with positions of Medsafe, the US-FDA and the MHRA (NB. certain codeine products may be purchased in these countries without a prescription). The conclusion was that the risks of respiratory depression and possible death in the context of ultra-rapid metabolism associated with codeine outweigh the benefits of codeine for all indications in children under the age of 12 years and that the risks to breastfed infants associated with ultra-rapid metabolism of codeine by their mothers outweigh the benefits of codeine for any indication by breastfeeding mothers. The committee was **undecided** whether the risks associated with ultra-rapid metabolism of codeine outweigh the benefits of codeine for any indication in ultra-rapid metabolisers of any age.

Sufficient label warnings excluding the use of these high risk populations are an appropriate measure and are a measure that is used by regulators with similar standards in other countries. It is not appropriate to suggest significant scheduling changes as a means to address this concern relating to ultra-rapid metabolisers, especially when the experts within ACSOM still remain undecided.

Delegate's Comment:
Changing the labelling and decreasing the pack size will not adequately address the problem of misuse and dependence.

Response:
[redacted] contends that this comment is not based on evidence.

Labelling and pack size restrictions have proven to be an effective risk mitigation measure for various product categories in Australia and in many other countries.

[redacted] also argues that this comment is not relevant in the context of codeine containing cold and flu preparations as there is **no evidence of abuse, misuse, dependence or toxicity in this category**.

The conclusion that there is an emerging and growing problem of codeine abuse appears to have been derived from a number of sources. We query the conclusions of the Delegate in respect of misuse of codeine containing analgesics in light of these sources generally. In particular, these sources do not provide any evidence to support any change in respect of codeine containing cold and flu products. These are discussed below.

The National Opioid Pharmacotherapy Statistics 2013
The National Opioid Pharmacotherapy Statistics consider only codeine containing analgesics, not codeine containing cold and flu preparation. The Nielsen *et al*. 2010 paper which is referenced in the survey also only refers to codeine containing analgesics. However, it is not clear from the statistics whether use of codeine containing analgesics is actually increasing since the 2009 NDPSC decision to up-schedule these products from S2 to S3. The paper states that the number of people receiving opioid pharmacotherapy treatment (clients) almost doubled between 1998 (from around 25,000) and 2013, but growth in client numbers slowed in recent years (to less than 1% a year from 2010–2013). On a snapshot day in June 2013, 47,442 clients were receiving opioid pharmacotherapy treatment in Australia, an increase of 745 from 2012. Client numbers grew slightly (by less than 1% annually) between 2010 and 2013 (The Australian population growth rate during this period ranged between 1.4 - 1.7% per annum) – the increase in clients receiving opioid therapy between 2010 and 2013 was less that the population growth rate. Although total number of clients had not decreased, the number of clients as a percentage of the population would have decreased.

Based on the above, in reference to OTC codeine analgesics it is not clear whether as a drug of dependence had actually increased since the NDPSC scheduling decision to up-schedule these products to Schedule 3 in 2009. This is a critical factor that needs to be addressed before any drastic scheduling decisions can be made.

Pilgrim *et al* - Fatal misuse of codeine–ibuprofen analgesics in Victoria, Australia[3]

Pilgrim *et al* authored a letter to the editor of the Medical Journal of Australia in 2013. This letter details results from a review of post-mortem results from the period of 1 January 2001 to 31 December 2011. The decision to up-schedule codeine containing analgesics became effective on the 1st May 2010, at which time there was a significant drop in sales/demand/supply of codeine containing analgesics shown in Figure 1 (this was presented as part of the [redacted] submission dated 7th May 2015). **This means that in the Pilgrim *et al* study, only 19 of the 132 months in the study period (14%) were covering the period in which the access to codeine containing analgesics were more restricted, raising questions over the validity of the recommendations in the letter.**

Further, the references cited by Pilgrim *et al* in support of the apparent increased abuse of OTC were published in 2010 and 2012, and these too would have been largely based on data collated prior to the enforced restricted access was in place with the up-scheduling of codeine containing analgesics.

Importantly, Pilgrim makes no reference to codeine containing cold and flu products, hence this data cannot legitimately be used to support the up-scheduling of codeine containing cold and flu products.

Roxburgh *et al* - Trends and characteristics of accidental and intentional codeine overdose deaths in Australia[4]

The Medical Journal of Australia published an article by Roxburgh *et al* days after the publication of the Delegate's interim decision. The publication of Roxburgh stated the data review period was from 2000 to 2013. Interestingly, Roxburgh only reported on the (increased) rate of codeine related deaths from the period of 2000 to 2009 (prior to the effective date of the up-scheduling of codeine containing analgesics). This conclusions aligns with the conclusions of Pilgrim *et al* above (Pilgrim was a co-author on the Roxburgh paper). Given the data analysis was from 2000 to 2013, **why was the rate of codeine related deaths between 2009 and 2013 not reported**. This appears to be an obvious scientific gap in the publication.

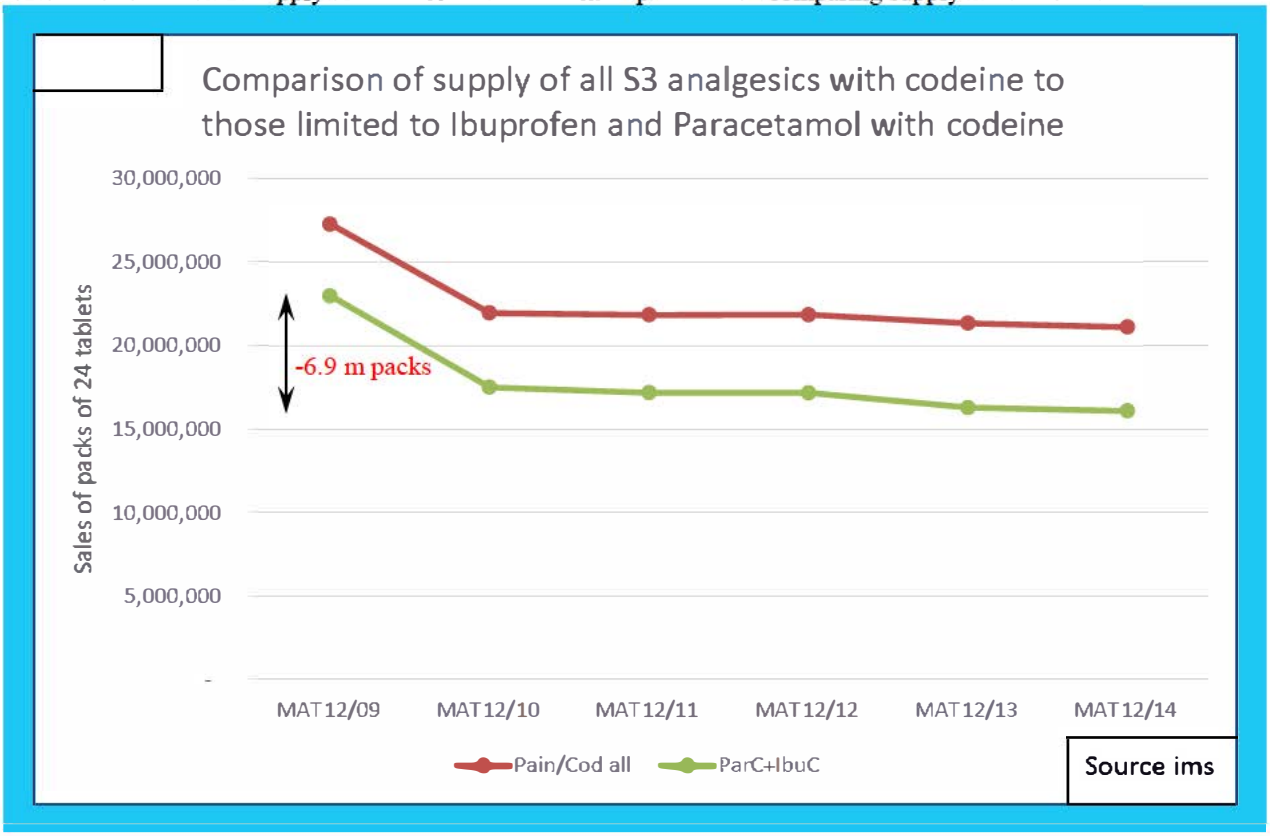
Roxburgh also concludes that *"Codeine-related deaths (with and without other drug toxicity) are increasing as the consumption of codeine-based products increases"*. IMS data clearly demonstrates that since the up scheduling of codeine containing analgesics in 2010, there has been a significant decrease in overall sales of codeine containing analgesics. This data does not support the conclusion from Roxburgh that codeine consumption is increasing.

Importantly, Roxburgh makes no reference to codeine containing cold and flu products, hence this data cannot legitimately be used to support the up-scheduling of codeine containing cold and flu products.

[3] Pilgrim, Dobbin & Drummer (2013) Fatal misuse of codeine–ibuprofen analgesics in Victoria, Australia. MJA 199(5) 329

[4] Roxburgh *et al* - Trends and characteristics of accidental and intentional codeine overdose deaths in Australia Med J Aust 2015; 203 (7): 299.

Figure 1 compares the total supply of S3 analgesic containing codeine products (Pain/Cod all) to the supply of products containing only paracetamol with codeine & ibuprofen with codeine (ParC + IbuC). The products most affected by the May 2010 change in scheduling of OTC analgesics with codeine have been paracetamol with codeine and ibuprofen with codeine. The reduction in supply of ParC+IbuC is 6.9 million packs when comparing supply in 2009 to 2014.



Other Data within the public submissions

In the public submissions, there was some support for the up scheduling of codeine containing products. Some of the publications, including a submission from the coroner from the state of Victoria, provided case studies of deaths related to (at least in part) to codeine abuse. All of the case studies provided in the public submission related to analgesics, not cold and flu products. Further, none of the case studies identified dates at which the abuse occurred. The Coroner acknowledges the contributions that Dr Pilgrim made in the preparation of the submission. It is not unreasonable to suspect that the cases of abuse reported by the coroner was prior to the up-scheduling of codeine containing analgesics (an issue highlighted above).

With regard to the case studies, there are no references to codeine containing cold and flu products in any of the public submission; hence the data in the public submissions cannot legitimately be used to support the up-scheduling of codeine containing cold and flu products.

Delegate's Comment:
Current labelling and packaging include insufficient warnings, and that there should be clear warning labels stating the risks of addiction and dependence, the risks of harm from the paracetamol or ibuprofen, and the risk of death. Access to codeine in Australia is inconsistent, in that the total amount of codeine available in a pack of Panadeine Extra ® (40 tablets containing 15mg each) is the same quantity as that available in a pack of codeine phosphate (20 tablets containing 30mg each), which is included in Schedule 8 and recognised to have potential for abuse or addiction.

[redacted] **Response:**

This is weighted towards codeine containing analgesics and not applicable to codeine containing cold and flu preparations. The TGA has failed to differentiate issues for the two groups which is critical given the significant differences in risk. Based on this, the above conclusion is irrelevant in relation to cold and flu products.

Nevertheless [redacted] does not dispute that there should be adequate warnings stating the risk of addiction and dependence despite the lack of evidence to suggest that it is on the increase since the NDPSC decision in 2009. In fact, as mentioned above, [redacted] products already include such warnings. For OTC products, this could be managed effectively through RASML warning statements in line with other jurisdictions as highlighted above. The proposed up-scheduling is not justified.

Furthermore the inconsistency around the availability of codeine is not applicable to codeine containing cold and flu preparations. The threshold for Schedule 2 medicines containing codeine is 10 mg or less of codeine per dosage unit.

Delegate's Comment:
Some sources, including the [redacted] product information, suggest or imply that before taking codeine a person should know their CYP4502D6 status, and this in turn means that no person should be able to self-administer codeine that has been obtained OTC. It is argued that the benefit of medical supervision that would be obtained with a rescheduling to S4 includes the ability of the prescriber to discuss with the patient the risks of excessive opiate effect, and provide advice about actions to take if this occurs. This argument applies equally well to products currently available in both S2 and S3.

[redacted] **Response:**

As noted above the population at greatest risk with ultra-metabolisers include children and breastfeeding mothers. This risk can be, and with respect to [redacted] is addressed, through warnings in labelling.

There is no conclusive evidence that the risk applies to all populations and all age groups to warrant such a significant scheduling change. Furthermore, the example above about patients knowing their CYP450D6 status relates to a company initiated change and therefore whether the warning statement is actually more conservative than what is required could be asked given the body of evidence

regarding ultra-metabolisers. The fact remains that CYP2D6 ultra-metabolisers are not confirmed as a high risk factor for all populations and all age groups. Jurisdictions that permit certain codeine containing products to be purchased without a prescription (US, Canada, Japan, UK, New Zealand) have addressed this risk through mandatory labelling and/or prescriber information.

Delegate's Comment:
Increasing amount of evidence for harm from abuse.

Response:
This evidence does not relate to codeine containing cold and flu products and therefore is not applicable. Details about sources of evidence have been provided above.

There is no evidence of harm in this category. The risk profile has not changed since the decision was made by the NDPSC in 2009 that the Schedule 2 remains appropriate.

Delegate's Comment:
Codeine is emerging as an increasingly commonly used drug of abuse internationally and in Australia. Data from the national opioid pharmacotherapy statistics in 2013 showed that codeine was the opioid drug of dependence for 1,038 clients receiving opioid substitution pharmacotherapy. The actual number was likely to be higher than this because of missing data. Another recently published study of 902 people who inject illicit drugs found that about one third had misused OTC codeine during the preceding six months.

Response:
As detailed above, the National Opioid Pharmacotherapy Statistics 2013 refer only to OTC codeine containing analgesics **therefore is not applicable to codeine containing cold and flu products**. The drugs clients receive treatment for include a range of drugs of dependence, including illicit opioids (such as heroin) and pharmaceutical opioids, which are available illicitly, by prescription (such as morphine and oxycodone) or over-the-counter (such as codeine–paracetamol combinations).

This report makes **no mention** of codeine containing cold and flu preparations. Consequently, it would be incorrect to use this data as a legitimate reason for up-scheduling cold and flu products containing codeine.

The Nielsen *et al.* 2010 paper which is referenced in the survey also confirms this fact. The scale of the alleged abuse problem is poorly understood and research is needed to quantify the scale of abuse, evaluate interventions and capture individual experiences, to inform policy, regulation and interventions.

Delegate's Comment:
Misuse of OTC codeine products including deaths resulting from hepatic injury, gastrointestinal perforations, hypokalaemia and respiratory depression.

[redacted] Response:
[redacted] again reiterates that there is no evidence that misuse of codeine containing cold and flu products have resulted in death, hepatic, gastrointestinal perforations, hypokalaemia or respiratory depression.

Delegate's Comment:
Genetic influence on codeine's action complicates risk and benefit decisions, and leads to questions regarding the role of codeine in clinical practice.

[redacted] Response:
This is an opinion and is not an evidence based comment. As detailed above, ACSOM, the FDA, MHRA and Medsafe have all concluded that the risks of respiratory depression and possible death in the context of ultra-rapid metabolism associated with codeine outweigh the benefits of codeine for all indications in children under the age of 12 years and that the risks to breastfed infants associated with ultra-rapid metabolism of codeine by their mothers outweigh the benefits of codeine for any indication by breastfeeding mothers. ACOSM was undecided whether the risks associated with ultra-rapid metabolism of codeine outweigh the benefits of codeine for any indication in ultra-rapid metabolisers of any age, and to date no other jurisdictions to our knowledge have taken such significant scheduling measures for all populations and age groups.

The TGA has the opportunity to take the same approach as Medsafe and similar regulators (as detailed above), and contraindicate use for the populations at greatest risk (risk based approach). Until such time there is solid evidence to support that risk of ultra-rapid metabolisers is applicable to all populations and age groups, then sufficient labelling warnings to exclude the use of populations at most risk is an appropriate measure. Furthermore the greatest risk has been when codeine analgesia has been used post operatively on children, for which we agree that that they should be contraindicated.

Delegate's Comment:
An appropriately qualified practitioner needs to assess the risk before making the decision that codeine will be used.

[redacted] Response:
Given the years of safe use of codeine containing cold and flu products and in the absence of evidence to suggest there is a misuse/abuse issue with codeine containing cold and flu products, there are questions of applicability of this comment to the cold and flu category.

In support of the years of safe use, the period from January 2010 until the end of April 2015, approximately 21 million packs of codeine containing [redacted] (24 dosage units) per pack were sold. This equates to close to 500 million individual dosage units and an average of 3.8 million packs per year (pack size of 24), yet to date there have been no reports of respiratory depression or death as a result of codeine overdose or ultra-rapid metabolisers.

Given the above evidence, it is difficult to justify the applicability of the comment above to the cold and flu category.

If for arguments sake, people were to attend a general practice for a standard level B consultation to get access to effective symptomatic relief for cold and flu, the potential cost to the taxpayer is an additional $87 million per annum. This is not to mention the cost to the consumer if the GP does not bulk-bill, and the potential for inappropriate antibiotics to be prescribed in this care setting. Further, there is a current campaign that is run by the South Eastern Sydney local health district (NSW Department of Health) about "*Saving our emergency departments for emergencies*". Within this campaign, coughs, cold and flus are called out as conditions that could adequately be managed by other healthcare service providers, such as pharmacists. Clearly this campaign is being run as people with these conditions are currently and inappropriately presenting themselves at emergency departments for what are minor and self-limiting ailments.

If access to effective and safe medication for these episodic, self-limiting conditions is further restricted, it could lead to an increase in the inappropriate presentation of patients to emergency departments and also result in unnecessary increase in antibiotic use. At a time when the Federal Government has been seeking to control unsustainable growth in utilisation of GP services to balance the Federal Budget, the idea of driving people with colds and flus into see a doctor at the taxpayer's expense is both contradictory and bad policy.

Delegate's Comment:
A recently released combination of two non-opioid analgesics (ibuprofen plus paracetamol) appears to be more effective than the CCAs, with a number needed to treat (NNT) of 1.5. This combination would fill any gap left by the unavailability of CCAs over the counter, giving consumers access to a more effective analgesic without requiring a prescription and without the risks of the marked variability in pharmacokinetics or abuse potential that are associated with codeine.

[redacted] Response:
This reason is not applicable to codeine containing cold and flu preparations; it is only applicable to codeine containing analgesics, therefore irrelevant. There is no such alternative "stronger" pain combination available for the short term symptomatic relief of cold and flu.

It is interesting that the TGA is suggesting that that the ibuprofen/paracetamol combination would fill any gaps left by the unavailability of CCAs over the counter. It should be pointed out that there is a population for whom either ibuprofen or paracetamol are not suitable. This small population of people are unlikely to have an option for treating strong pain (above single active therapy), without out being forced to see a medical practitioner for a prescription, with the likely outcome of a prescription of stronger pain medication being prescribed such as oxycodone or tramadol. One questions whether this would be the best outcome for the patient from a risk benefit perspective.

Further since the registration of this combination, numerous submissions have been made to have the combination included in Appendix H of the SUSMP. None of these applications have been successful so this combination cannot be advertised to consumers. This means that consumers are unaware of this product as an alternative. Pharmacists are very familiar with codeine combinations; they have been on the market for many years. With the current scheduling and lack of awareness of the ibuprofen plus paracetamol combinations, they are not the immediate option that the paper suggests

Delegate's Comment:
Potential unintended consequences and disadvantages of a decision to reschedule CCAs to S4 need to be considered. One would be a reduction in the availability of analgesics for moderate to severe pain, although the evidence suggests that the addition of codeine adds only a minor additional analgesic effect over and above that of the ibuprofen or paracetamol in the combination product. The recent introduction of a paracetamol/ibuprofen combination may fill this niche more effectively than the CCAs have done, without the disadvantages of codeine. A reduction in the availability of a drug known as an anti-tussive agent, despite the lack of evidence available to support this, would also occur, but significant actual disadvantages are unlikely to occur. No other potential disadvantages to the community are readily identified.

[redacted] **Response:**

This evidence does not relate to codeine containing cold and flu products and therefore is not applicable. Nevertheless [redacted] would like to highlight The comment makes an incorrect assumption that cold and flu preparations containing codeine do so on the basis for preventing cough. The prevention of cough is **not** a TGA approved indication for codeine containing cold and flu products. Any decision that is made upon the basis that codeine's role in cold and flu products is for anti-tussive purposes raises questions as to the legitimacy and validity of the decision, as it has been based upon an incorrect assumption.

As mentioned, there is evidence of effectiveness of codeine-paracetamol combination, the substitution of a paracetamol/ibuprofen combination is not appropriate for cold and flu products, and millions of consumers rely on the ingredients in the cold and flu products for relief of their short-term symptoms. This is further supported by its established use, given this combination is used by millions of Australians annually.

Further unintended consequences for codeine containing cold and flu remain the negative economic impacts to the patient and the public health system by potentially driving cold and flu sufferers into GP clinics (or emergency rooms) unnecessarily, for symptomatic relief.

This, in turn will increase the cost to the consumer of accessing cold and flu medicines and place undue pressure on the GP with extra patient load and potential for inappropriate antibiotic prescribing. The potential cost to the taxpayer is likely to be an additional $87 million per annum.

Furthermore, the up-scheduling of codeine-containing cold and flu medicines to S4 respectively, is likely to increase demand for the PSE formulated cold and flu products still available in Pharmacy. The result would be greater volumes of PSE in the market than we see today and greater pressures on both pharmacy and law enforcement to track sales.

The current evidence clearly demonstrates that the current scheduling of cold and flu products with codeine is appropriate. No new evidence has emerged since the scheduling decisions in 2009 to support a scheduling change.

Delegate's Comment:

The major impact on public health of the proposed amendment would be a reduction in the risk to those individuals who, unbeknownst to themselves, have a rapid metaboliser phenotype of CYP4502D6 and are therefore at significant risk of excessive morphine concentrations following ingestion of usually recommended doses of codeine for any indication

Delegate's Comment:

Codeine is an opioid which must be metabolised by CYP2D6 to its active metabolite, morphine, for its analgesic effect. Different genetic groups show significant variations in metabolism of codeine. Of

particular concern are "ultra-rapid" metabolisers, where the accelerated metabolism of codeine to morphine results in an increased risk of morphine toxicity and adverse events.

Delegate's Comment:
The function of the enzyme carrying out that transformation is genetically controlled and highly variable between individuals because of the existence of multiple forms of the relevant gene; the difference in exposure to morphine following a standard dose of codeine can be up to 45-fold higher in ultra-rapid metabolisers compared with poor metabolisers.

[redacted] **Response:**
This issue has been addressed in earlier points. The risk/profile of the cold and flu preparations containing codeine has not changed since the NDPSC decision in 2009. Codeine in current levels in [redacted] has been available for a very long period of time (since at least [redacted] and there is no evidence of harm as suggested by the Delegate coming to individuals that have taken these products. On the contrary, there is a long history of safe use with approximately 3.8 million packs of codeine containing [redacted] sold annually and no reports of individuals coming to harm. Further, the high risk populations are contraindicated for use, further mitigating any risk associated with these populations.

As previously mentioned, the ACSOM still remain undecided whether the risks associated with ultra-rapid metabolism of codeine outweigh the benefits of codeine for any indication in ultra-rapid metabolisers of any age. Until such time there is solid evidence to support this position, then sufficient labelling warnings to exclude the use of populations at most risk is an appropriate measure. This should not be a consideration at this point in time.

Further, it is difficult to compare the levels of morphine produced in rapid metabolisers against levels of morphine in poor metabolisers. Comparisons should be made between the ultra-metabolisers, the extensive metabolisers, the intermediate metabolisers and the poor metabolisers, not just the extreme groups.

Delegate's Comment:
Ultra-rapid metabolisers are therefore at risk of morphine overdose, with potentially fatal consequences, following "usual" doses of codeine.

[redacted] **Response:**
The "usual" doses of codeine in cold and flu products are less than the levels of codeine in primary combination analgesics. The risk associated with ultra-metabolisers is dose dependant – the final concentration of morphine produced by the demethylation of codeine is dependent on the concentration of the initial substrate (codeine) (typically 0-15% of codeine is de-methylated to produce morphine). It is difficult to understand how the comment applies equally to analgesics and cold and

flu products. This is scientifically illogical given the difference in codeine concentrations in these products.

Delegate's Comment:
Individuals rarely know their metaboliser status, and testing is not readily available.

[redacted] Response:
Until there is evidence to show that the metaboliser status is critical to ensure safe use by a consumer of codeine containing cold and flu preparations of all populations and age groups then this reason is not appropriate. This is further supported by the fact that there is no evidence of harm to individuals that have consumed these products, therefore we do not believe knowing this status necessarily adds value for all populations and age groups.

If this is a genuine concern for public health, the question should be raised whether there will be screening of metaboliser status of patients prior to use of **any** opioids that are converted to morphine when visiting GP's? Given that opioids are the cornerstone of pain management in oncology patients, the cost to the public health system will be profound if such a measure became necessary.

Delegate's Comment:
All other opioids are at least Schedule 4.

[redacted] Response:
Not all other opioids are at least schedule 4. The above statement is factually incorrect. Opioids that are not in Schedule 4 include dihydrocodeine, pholcodine and loperamide (a non-absorbed opioid compound).

This statement is applicable to opioid analgesics with greater efficacy when compared with codeine. This is not a reason to up-schedule all opioids to Schedule 4. This logic has never been a consideration in the scheduling of substances. If this was the case, no medicine would ever be down-scheduled (e.g. PPIs that have moved from S4 through to S2 for pantoperazole and esomeprazole – would have always stayed S4 because all other PPIs are S4). Furthermore, the Delegate should make the decision based on codeine and its specific uses and characteristics, which are not identical to other opioid analgesics (e.g. use in small doses for treatment of cold and flu).

Delegate's Comment:
The approved indication for the S3 codeine products is for the "temporary relief of strong pain and discomfort associated with a number of different medical conditions". It is noted that there is significant use of S3 codeine products for longer term relief of chronic pain and a number of public submissions by consumers have noted that this is how they use it.

[redacted] **Response:**
This comment does not relate to cold and flu preparations.
[redacted] would like highlight that there are other S3 codeine containing products that are not used for strong pain. This includes the cold and flu preparations that contain codeine which include as a decongestant the Schedule 3 active, pseudoephedrine. The products are not indicated for the temporary relief of strong pain. As noted in earlier points, it has been established by the NDPSC in 2009 that long term use is not a consideration for cold and flu products. Cold and flu medicines are for short-term, episodic, self-limiting conditions. Consumers use these products only as long as they are suffering symptoms of cold and flu. This is typically less than 3 days, therefore by virtue of their indications and patterns of use, **they are not a likely to be taken for chronic conditions**.

[redacted] preparations containing codeine have been used responsibly by millions of Australians and New Zealanders appropriately for over 40 years.

Delegate's Comment:
The management of chronic pain would be better achieved by having medical practitioner input with appropriate advice on non-medicine treatments and appropriate medicinal treatment for the chronic pain, rather than self-treating with long term codeine containing analgesics (CCAs).

[redacted] **Response:**
This comment does not relate to cold and flu preparations. [redacted] offers no response to this comment apart from the fact that this does not support the up scheduling of cold and flu products that contain codeine.

Delegate's Comment:
The presence of codeine in OTC combination analgesics contributes to severe adverse outcomes associated with over-dosage of the paracetamol or ibuprofen component, because the development of dependence on codeine leads to overuse of the combination. Anecdotally some abusers of OTC codeine products are consuming 30 to 70 tablets/capsules per day of the CCAs.

[redacted] **Response:**

This comment does not relate to cold and flu preparations. [redacted] offers no response to this comment apart from the fact that this does not support the up-scheduling of cold and flu products that contain codeine.

Delegate's Comment:

In Europe codeine is not an OTC medicine (i.e. is a prescription only medicine at least) in 13 countries being Austria, Belgium, Croatia, the Czech Republic, Finland, Germany, Greece, Italy, Luxembourg, Portugal, Slovakia, Spain and Sweden.

Delegate's Comment:

Codeine is also a Prescription Medicine in the USA, Hong Kong, Iceland, India, Japan, the Maldives, Romania, Russia, and the United Arab Emirates.

[redacted] **Response:**

It is disappointing that a number of countries with regulators that the TGA benchmark against, were absent from the list in the above comments. Equally disappointing is the fact that a number of the countries listed above are listed incorrectly.

Countries where codeine is found as an OTC medicine include

- United Kingdom
- France
- Canada
- New Zealand
- Japan (restricted to one product per transaction)
- United States of America.

For the USA, Schedule V drugs, substances, or chemicals are defined as drugs with lower potential for abuse than Schedule IV and consist of preparations containing limited quantities of certain narcotics. Schedule V drugs are generally used for antidiarrheal, antitussive, and analgesic purposes and are available without a prescription. While Schedule V codeine products **may** be sold without a prescription from behind the pharmacy counter by a pharmacist only according to Federal and some state laws, in practice, largely due to the retail environment in the US, this dispensing opportunity is not utilized to its full extent.

The regulatory status of codeine in other markets should be considered, however, comparison between the scheduling framework and the retail environment should also be taken into consideration.

Delegate's Comment:

There is no evidence that low dose codeine combination analgesics provide any additional analgesia over optimal dosing of paracetamol, aspirin or ibuprofen.

Response:

This is an erroneous statement. Cochrane reviews of paracetamol plus codeine[5] and ibuprofen plus codeine[6] have established that these combinations are effective. Also, clinical studies demonstrate that codeine-containing combination analgesics at OTC doses are more efficacious than placebo[7,8] or single ingredient analgesics.[9,10,11]

Delegate's Comment:

In February 2009 NDPSC decided that:

- Based on the currently available information from Australia, the evaluator concluded that there was potential for significant harm from OTC combination analgesics containing codeine (CACC) and even death, and it was not possible to accurately estimate the associated risk, although the following were reasonably assumed:
- The proportion of all users that abuse OTC CACC is low.
- The risk of harm among all users of OTC CACC is low.
- The risk of harm among abusers of OTC CACC is high.

Central consideration in allowing OTC supply of codeine combinations was that the benefits outweighed the risks and therefore asserted that the insufficient data on efficacy may mean that the benefits no longer outweighed the risks. While agreeing that efficacy remains important to any case justifying OTC supply of codeine, the Committee noted the Codeine Working Party advice that there was not sufficient information available to the Members at this time to resolve the question of codeine efficacy at ≤ 30mg

DelegateDelegate's Comment:

The NDPSC rescheduled OTC codeine-containing combination analgesics to Schedule 3 in 2010, with the aim of increasing surveillance of codeine medication usage by pharmacists to ensure quality use of medicines, as it was recognized that there is a potential for harm if used inappropriately. The Schedule 3 entry included limits on the maximum daily dose and pack size, and restrictions on the quantities of codeine in divided (and undivided) preparations.

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[5] Toms L, Derry S, Moore RA, McQuay HJ. Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. *Cochrane Database Syst Rev* 2009;(1):CD001547.

[6] Derry S, Karlin SM, Moore RA. Single dose oral ibuprofen plus codeine for acute postoperative pain in adults. *Cochrane Database Syst Rev* 2013;3:CD010107.

[7] Frame JW, Fisher SE, Pickvance NJ, Skene AM. A double-blind placebo-controlled comparison of three ibuprofen/codeine combinations and aspirin. *Br J Oral Maxillofac Surg* 1986 April;24(2):122-129.

[8] Daniels SE, Goulder MA, Aspley S, Reader S. A randomised, five-parallel-group, placebo-controlled trial comparing the efficacy and tolerability of analgesic combinations including a novel single-tablet combination of ibuprofen/paracetamol for postoperative dental pain. *Pain* 2011 March;152(3):632-642.

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[10] Comfort MB, Tse AS, Tsang AC, McGrath C. A study of the comparative efficacy of three common analgesics in the control of pain after third molar surgery under local anaesthesia. *Aust Dent J* 2002 December;47(4):327-330.

[11] Macleod AG, Ashford B, Voltz M, Williams B, Cramond T, Gotta L, Simpson JM. Paracetamol versus paracetamol-codeine in the treatment of post-operative dental pain: a randomized, double-blind, prospective trial. *Aust Dent J 2002* June;47(2):147-151.

[redacted] **Response:**

This additional risk from abuse in the risk/benefit analysis is **not relevant for codeine containing cold and flu preparations**. There is evidence of efficacy of codeine paracetamol combinations (see previous comment).There is no change to the risk benefit position since the 2009 NDPSC decision with respect to cold and flu products which is the primary consideration under Section 52E of the Act.

It is important also to note that the up-scheduling of codeine containing analgesics had the impact of reducing volume and sales of these products. Work conducted by [redacted] demonstrated that there was no transference of abusers from the analgesic category to the cold and flu category.

Unfortunately, no research has been conducted that compares the rate of abuse/dependency pre and post the scheduling decision for codeine containing analgesics therefore any conclusions drawn are hypothetical and not evidence based.

Delegate's Comment:

Rescheduling to Schedule 3 has not achieved the required reduction in harm to affected individuals. Since the rescheduling of codeine from 2010 there hasn't been the reduction in risk that might have occurred.

[redacted] **Response:**

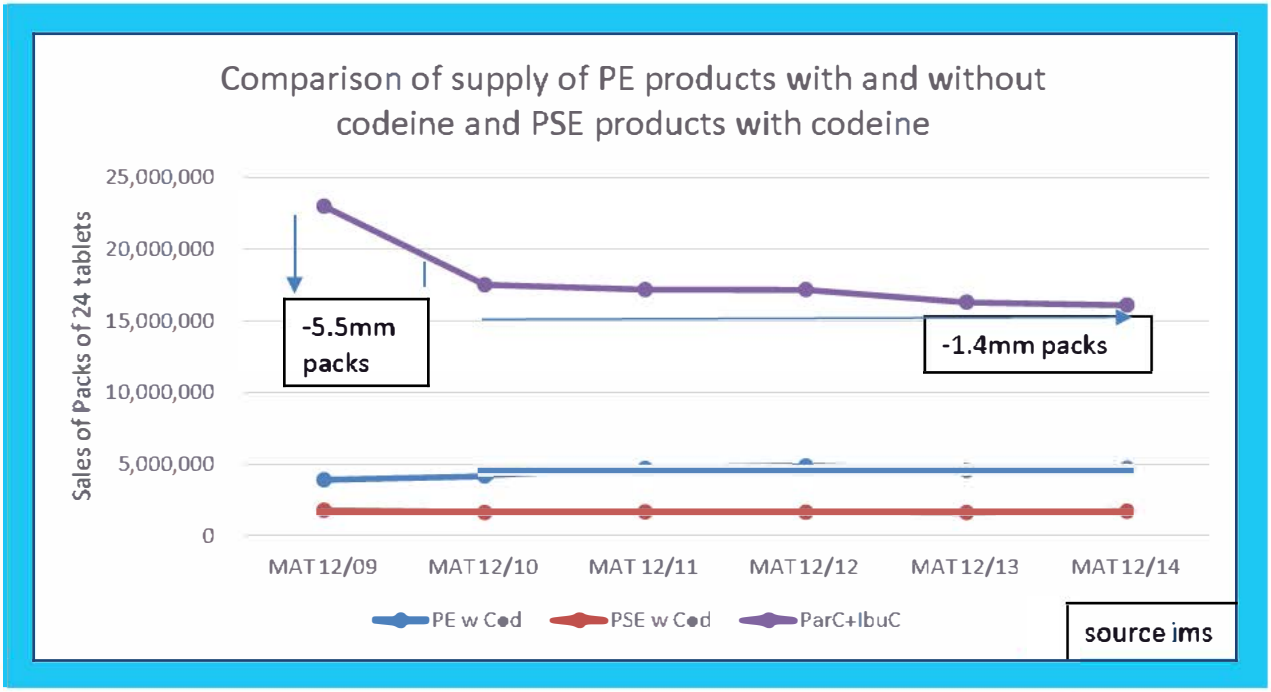
There is no robust evidence to substantiate this comment. This is not relevant for codeine containing cold and flu preparations.

However as highlighted above, evidence provided by Pilgrim *et al* and Roxburgh *et al* did not include an analysis pre and post the up-scheduling of codeine containing analgesics in 2010. Without this analysis, the success or failure of the up-scheduling cannot be concluded with any scientific rigour, as would be required by an evidence based regulator. Conclusions without this analysis are purely speculative, based on anecdotal data.

In the [redacted] submission of 7th May 2015, data relating to the volume of individual packs of non-prescription analgesics and cold and flu products supplied through pharmacy clearly demonstrate that there has been no transfer of demand from non-prescription analgesics containing codeine to cold and flu products containing codeine. The NDPSC previously expressed a concern that this may occur when codeine containing analgesics were up-scheduled from S2 to S3 in 2009; however, as noted, there has been no evidence that this has occurred.

This unequivocally demonstrates that the abuse/misuse risk profile of codeine containing cold and flu preparations has not changed since the up-scheduling of codeine containing analgesics. For ease of review, the data is again provided below.

Figure 2 demonstrates clearly that the fall in supply of ParC/IbuC by -5.5 million packs between 2009 and 2010 did not influence supply of PE w Cod or PSE w Cod over that period. The progressive decline by a further 1.4 million packs between 2010 and 2014 also appears to have had no influence on supply of PE w Cod nor PSE w Cod. This data clearly negates the concern expressed by the former NDPSC about the potential for a transfer of demand from S3 analgesics with codeine to S2 PE with codeine. Thus there is no requirement that consideration be given as to whether the Schedule 2 entry for codeine should also be amended.



Delegate's Comment:

Codeine is increasingly a drug of abuse in Australia, and some individuals have developed severe adverse effects from the high doses of paracetamol and ibuprofen that accompany the use of large numbers of tablets in a codeine-dependent person. A pack of CCA available under S3 contains the same total dose of codeine as a pack of codeine available only under S8.

[redacted] **Response:**

This is not relevant for codeine containing cold and flu preparations. This comment relates specifically to codeine containing analgesics. [redacted] does not dispute that there are instances of codeine abuse/misuse. There is also no dispute that there are individuals who have suffered severe adverse events from high doses of ibuprofen, however there is no evidence to suggest inappropriate use of codeine cold and flu preparations has increased since the NDPSC 2009 decision. The vast majority of consumers use codeine products responsibly and as directed and do not suffer the severe adverse events from excessive amounts of either paracetamol or ibuprofen.

It is difficult to understand how a conclusion can be drawn that codeine abuse is an increasing problem in Australia without robust evidence. Scientific evidence that is in the public domain does not include an analysis of abuse rates or death rates pre and post the up-scheduling of codeine containing analgesics in 2010.

Further there is no evidence of abuse in cold and flu products containing codeine, in fact all of the evidence supports the fact that codeine containing cold and flu products are used safely with no serious adverse events.

Delegate's Comment:
Since OTC CCAs were rescheduled to Schedule 3 in 2010, industry and pharmacy organisations have not been able to fully address concerns regarding codeine dependence.

[redacted] **Response:**

This is not relevant for codeine containing cold and flu preparations, and a clear distinction should be made between codeine containing cold and flu preparations and codeine containing analgesics. The concerns of codeine dependence relate to codeine containing analgesics given pain management is both acute and chronic, whereas cold and flu symptoms are self-limiting and short in duration. However sponsors and the general public were not sufficiently informed of the evidence that suggests that codeine abuse of analgesics has increased, nor appropriately managed since the NDPSC decision to up-schedule codeine containing analgesics to Schedule 3. The former NDPSC was concerned that with the up-schedule of codeine containing analgesics to Schedule 3 thus more restricted supply of codeine, there would be transference of dependence from analgesics to Schedule 2 cold and flu products. It was noted by the NDPSC that this should be monitored, however to date there has been no evidence to suggest that there has been any transfer of dependence to these products.

The NDPSC was disbanded after the scheduling decisions were made for codeine, and as a result, no formal requests by the TGA or the ACMS were ever made to assess the impact on the potential for transference. However in the Delegate's reasons for final decisions in September 2011 on matters relating to cough and cold, the Delegate affirmed the NDPSC decision that there should be no change to the scheduling of codeine in cold and cough preparations.

Acknowledging its role as a major supplier in the cold and flu category, [redacted] decided to proactively monitor for any resulting changes to the demand of codeine containing cold and flu products in both Australia and New Zealand. In both 2014 and 2015, the Australian data was voluntarily shared with the TGA (Dr Larry Kelly & Dr Tony Hobbs) and with the Chief Pharmacist of the NSW State Department of Health (Bruce Battye). Data specific to New Zealand was shared with Medsafe (Sarah Reader) and other key stakeholders (June 2015). Summaries of this data were provided in the submission of the 7th May 2015.

Both the national and state data conclusively demonstrate that there is **no relationship between the fall in supply/demand of non-prescription codeine-containing analgesics and the demand for cold and flu products containing codeine**. There has been no unexplained increase in demand for these products. In fact, demand has remained relatively flat, with slight seasonal variances which is dependent on the severity of the cold/flu season. The data for New Zealand also shows similar trends

in the demand for codeine-containing cold and flu products (New Zealand re-classified codeine containing analgesics at a similar time to Australia).

In all stakeholder meetings, it was acknowledged that the data provided valuable insight into the success of the up-scheduling of codeine, that there had been no transference of misuse of analgesics to cold and flu containing products. There were no concerns as to gaps in the data collated.

This clearly shows that the NDPSC decision to differentiate and exclude the S2 cold and flu products with codeine from up-scheduling in 2009 was appropriate, and currently remains appropriate.

As no other concerns were raised by either the NDPSC of the ACMS, it is difficult to ascertain how this this data does not adequately address the codeine dependence issue (or lack of dependence, as the case is).

Delegate's Comment:
Codeine in the unit doses present in OTC products provides very little additional analgesic effect over and above that provided by the accompanying drug in the combination. It is also noted that there are new combination products with paracetamol and ibuprofen which are more efficacious than low dose CCAs.

Response:
In the June 2009 meeting of the NDPSC it was acknowledged by the Codeine Working Party (CWP) that *"the TGA had not evaluated efficacy data for any OTC product containing codeine. While efficacy data were critical to an assessment of overall risk-benefit efficacy per se was not a primary issue for consideration under section 52E. The CWP felt that the TGA was best placed to address questions about efficacy"*. Since that time there has been no change in the efficacy and no change to the risk since this time, the risk/benefit profile remains unchanged for codeine containing cold and flu preparations.

Furthermore, this is an erroneous statement. Cochrane reviews of paracetamol plus codeine and ibuprofen plus codeine have established that these combinations are effective. Also, clinical studies demonstrate that codeine-containing combination analgesics at OTC doses are more efficacious than placebo or single ingredient analgesics.

Lastly, as mentioned, the ibuprofen paracetamol combination is not particularly suitable for OTC cold and flu products.

Delegate's Comment:

CCAs do not meet the criteria required for Schedule 3, particularly that they are not "substantially safe in use but require professional advice or counselling by a pharmacist", and cannot be said to "not require close medical management." Rather, it would be more appropriate for CCAs to be prescribed so that consumers can be warned about the potential risks and adverse effects can be more closely monitored.

[redacted]**Response:**

This is not relevant for codeine containing cold and flu preparations. This comment specifically relates to codeine containing analgesics. It is a concern that there is an opinion that pharmacists are not capable of or do not warn patients of potential risks or adverse events.

Delegate's Comment:

Concurrently the Advisory Committee on the Safety of Medicines (ACSOM) has recently considered the risks of codeine use in children, and codeine use in persons who are ultra-rapid metabolisers of codeine. Excerpts from the meeting statement from ACSOM 28 state:

- ACSOM agreed that the risks of respiratory depression and possible death in the context of ultrarapid metabolism associated with codeine outweigh the benefits of codeine for all indications in children under the age of 12 years.
- As it is not possible to identify in advance the subgroup of children who are at increased risk of toxicity (e.g. through being an ultra- rapid metaboliser), the committee's advice relates to the risks for all children under the age of 12.
- ACSOM also agreed that the risks associated with codeine outweigh the benefits of codeine for analgesia in children under the age of 18 years who have undergone tonsillectomy or adenoidectomy for sleep apnoea, for the same reasons as for children under the age of 12 years, as above. This is consistent with the United States Food and Drug Administration (US FDA) position that codeine use after adenotonsillectomy is contraindicated. The committee also noted that there have been a number of adverse event cases observed that are not clearly explained but may relate to sleep apnoea.
- ACSOM also agreed that the risks to breastfed infants associated with ultra-rapid metabolism of codeine by their mothers outweigh the benefits of codeine for any indication by breastfeeding mothers as a mother's knowledge of her own experience with codeine (and indirectly, metaboliser status) does not predict the infant's response, breastfeeding should be a contraindication for codeine.
- ACSOM noted the following contraindications which were recommended in the TGA's safety review to be included in the codeine Product Information - use in children under the age of 12 for any reason; use in people of any age known to be ultra-rapid metabolisers; use in children younger than 18 years of age who have undergone adenotonsillectomy for obstructive sleep apnoea; and use by breastfeeding mothers.
- The committee noted that the OTC availability of codeine-containing medicines supported a general perception in the community that codeine is safe. Therefore, communication of the

contraindications by label changes alone was not likely to achieve the desired outcome of risk reduction. Additional measures including education and the possible rescheduling of codeine containing medicines also needed to be considered. The committee supported consistency and harmonisation in labelling across all codeine-containing medicines, especially regarding advice to breastfeeding mothers.

- Activities to reduce the use of codeine cannot occur in isolation from consideration of alternative pain management strategies. Pain management strategies that do not include codeine needed to be carefully defined and their implementation carefully considered. For example, direct administration of morphine could be considered as an alternative and the issues of analgesic polypharmacy and escalation up the 'pain ladder' also require consideration in the development of any pain management strategies that omit codeine.

[redacted] **Response:**

The issue relating to ultra-rapid metabolisers is discussed at length in points above. All issues raised by the Delegate can be addressed through effective labelling and contraindications. It is an assumption that effective labelling is not likely to achieve the desired outcome of risk reductions. Contraindicating its use to high risk populations does achieve the desired outcomes, and has for many OTC medications. Additionally, there has been no evidence of consumers taking [redacted] coming to harm due to an individual's codeine metabolic status further supporting this position

The ACSOM states that "*communication of the contraindications by label changes alone was not likely to achieve the desired outcome of risk reduction*". Whilst this is an opinion, the hypothesis that appropriate label changes will not mitigate the risks associated with codeine dependence has not been tested and arguably cannot be considered evidence to support the up scheduling of codeine contain OTC products. In fact, a number of jurisdictions with regulators of similar regulatory standards took the proactive approach to mandate warnings and contraindications that were consistent with the position of the ASCOM as early as 2012. No such warning or contraindications were mandated by the TGA.

Delegate's Comment:

It should be noted that the following factors for a Schedule 3 medicine in the Scheduling Policy Framework (SPF) are not met: – Codeine does not meet the SPF scheduling factors for inclusion in Schedule 3. In particular, criterion 2 is not satisfied – i.e. "The use of the medicine at established therapeutic dosages is not expected to produce dependency. Where there is a risk of misuse, abuse or illicit use identified, the risk can be minimised through monitoring by a pharmacist."

[redacted] **Response:**

This is not relevant for codeine containing cold and flu preparations. This comment relates specifically to codeine containing analgesics. There is no evidence of abuse or dependency of either Schedule 2 or Schedule 3 codeine containing cold and flu products. Consequently, it cannot be stated

that when codeine is combined with other actives for the purpose of providing temporary symptomatic relief of cold and flu it fails to meet the criterion for either Schedule 2 or schedule 3 medicines.

This reason cannot be used to support the up-scheduling of codeine containing cold and flu products.

Delegate's Comment:
Codeine containing analgesics should now be included in Schedule 4 because codeine meets the factors in the Scheduling Policy Framework required for Schedule 4, and particularly the following factors: – In particular, use at established therapeutic dosage levels may produce dependency (criterion 3). – Codeine also meets SPF Schedule 4 criterion 1 (diagnosis, management or monitoring of chronic pain conditions requires medical or dental intervention before use and, although OTC codeine products are intended for short-term use, many consumers use them for chronic pain without medical intervention) and criterion 7 (its use has contributed to, or is likely to contribute to, communal harm).

[redacted] Response:
This is not relevant for codeine containing cold and flu preparations. This comment relates specifically to codeine containing analgesics and is not relevant to codeine containing cold and flu products.

Delegate's Comment:
Other issues: – Codeine alone is ineffective as an analgesic in doses – If codeine is to remain in use as an analgesic, then the patient's metaboliser status needs to be ascertained prior to prescription or dispensing, however this is not practical.

[redacted] Response:
Codeine alone is not used in cold and flu products and efficacy should be reviewed from the risk/benefit perspective. Efficacy alone should be reviewed by the evaluation section of the TGA which has been highlighted by the NDPSC in 2009. However, given the long history of safe and responsible use of codeine containing cold and flu products in Australia, along with the contraindications for high risk populations, the risk profile of these products remains unchanged since the last review by the NDPSC in 2009 and the Delegate's affirmation in September 2011.

All decisions in relation to scheduling need to consider the factors listed under section 52E of the Therapeutic Goods Act 1989 (the Act). It is difficult to understand how the practicalities of assessing a patient's codeine metabolic status can be a factor for consideration in relation to the scheduling of codeine, especially in the absence of Adverse Event reporting in relation to this concern.

Delegate's Comment:
It was suggested that there were options to try and minimise the abuse related to CCAs by either expanding Project Stop or real-time monitoring of CCA use.

Delegate's Comment:
Project Stop relates to the monitoring of sales of pseudoephedrine and is a police related activity to prevent diversion of pseudoephedrine as a precursor for illegal methamphetamine manufacture.

Delegate's Comment:
The Project Stop website states its role as: – Project STOP is an initiative of the Pharmacy Guild of Australia to address the problem of precursor diversion through Australian Community Pharmacies. The most common precursor sourced through the community pharmacy channel is Pseudoephedrine which can be used in the illegal manufacture of methamphetamines. – Project STOP is an online tool which provides decision support to pharmacists who need to establish whether requests for products containing Pseudoephedrine are legitimate. It also assists pharmacists in meeting their state regulatory recording requirements where they exist.

Delegate's Comment:
Real-time monitoring of medicines is not currently in place in any jurisdiction other than Tasmania where it is restricted to S8 medicines. There is no formal implementation of real-time monitoring across Australia and whether its implementation would it is unsure whether it would ever come down to S3 medicines.

[redacted] **Response:**
This is not relevant for codeine containing cold and flu preparations. This comment relates specifically to codeine containing analgesics. Nevertheless, [redacted] believes there is merit in this recommendation for codeine containing analgesics ([redacted] having no vested interest in codeine containing analgesics).

Delegate's Comment:
Despite the risks of abuse identified when CCAs were up-scheduled in 2010 there has been no initiative to include CCAs into Project Stop prior to the application to up-schedule codeine to S4.

[redacted] **Response:**
This is not relevant for codeine containing cold and flu preparations. This comment relates specifically to codeine containing analgesics. Nevertheless, there only exists evidence to support a growing abuse and dependency problem with codeine containing analgesics up to the effective date of the up-scheduling of these products in 2010. There is no robust evidence to demonstrate that the concerns of abuse and dependency continued to grow or decreased post the up-scheduling decision.

The sales/demand of codeine containing analgesics declined post the up-scheduling. It would therefore be logical to suspect that the issue of dependency and abuse have also decreased. Again, until the analysis of medicine misadventure comparing pre- and post the up-scheduling of codeine containing analgesics, this is purely speculative.

Delegate's Comment:
In both Project Stop and real-time monitoring the onus on prevention of supplying CCAs would fall on pharmacists when dealing directly with consumers.

[redacted] **Response:**
This is not relevant for codeine containing cold and flu preparations. This comment relates specifically to codeine containing analgesics. However [redacted] believes that the onus is currently on pharmacists for pseudoephedrine. This situation should be no different for codeine containing analgesics.

This should not be considered to be a reason for up-scheduling codeine containing OTC products

Delegate's Comment:
Another option considered was decreasing the pack size of CCAs from the current limit of five days with a recommended daily dose not exceeding 100 mg of codeine to a pack size limit of three days' supply as has occurred in the United Kingdom. However decreasing the available pack sizes of OTC codeine products might help reduce the incidence of new users becoming dependent on codeine, but is unlikely to be effective for those who are already dependent.

[redacted] **Response:**
This is not relevant for codeine containing cold and flu preparations. This comment relates specifically to codeine containing analgesics. However [redacted] would like to point out that this comment represents an opinion and is not evidence based. Analysis of the impact that this pack size reduction has had on abuse rates in the UK should be completed before excluding the proposal.

Delegate's Comment:
A number of the pre-meeting submissions considered it unduly burdensome to require consumers to obtain a prescription for supply of codeine combination analgesics. However, pharmacists can recommend alternate pain relief products, such as a paracetamol-ibuprofen combination, or consumers could obtain a prescription (to have on hand when needed for acute pain) if they visit a general practitioner for any reason.

[redacted] Response:
This is not relevant for codeine containing cold and flu preparations. This comment relates specifically to codeine containing analgesics. However it should be pointed out that the burden highlighted above and in the pre-meeting submissions, also applies equally to codeine containing cold and flu products if they were to be made S4 medicines.

Purchase behaviour of consumers in the cold and flu category is not to stock pile - it is almost always a distressed purchase. Having a prescription on hand for codeine containing cold and flu products to facilitate this distressed purchase is not realistic or practical.

Delegate's Comment:
To be consistent with the interim decision to remove the S3 entry for codeine and for the issues around codeine in the 12 and under population as recommended by ACSOM the S2 entry should also be deleted. There are alternative OTC analgesic products for short-term pain relief.

[redacted] Response:
This is not relevant for codeine containing cold and flu preparations. This comment relates specifically to codeine containing analgesics. This comment relates to analgesics, yet the interim decision is to delete all entries for codeine in schedule 2 and schedule 3. This has the consequence for making codeine containing cold and flu products schedule 4 products.

The reasons of "issues around codeine in the 12 and under population" is not relevant as codeine containing cold and flu products are contraindicated for the high risk populations, such as children under the age of 12.

Additionally, there was no recommendation by the ACSOM to delete the schedule 2 entry for codeine – and there was certainly no recommendation to delete S2 or S3 entries for codeine where it specifically related to cold and flu products.

Cold and flu medicines containing codeine are responsibly used by millions of Australians appropriately opting for self-care of what are short-term, episodic and self-limiting conditions. The appropriate care setting for these treatments to be administered is community pharmacy.
There is no current or historical evidence of widespread abuse of cold and flu products containing codeine.

Retaining S2 codeine/phenylephrine combinations was a successful strategy for reducing the amount of pseudoephedrine in trade. Further restrictions on the availability of S2 codeine/phenylephrine combinations will negate this.

Restricted access to safe and effective codeine containing cold and flu products could drive people with colds and flus into general practice and emergency departments for access to care, which will have the consequences of a negative impact on the health budget at a time when over-utilization of medical services is very difficult to control and inappropriate use of antibiotics.
The potential for a significant consumer backlash given these products are widely used and the new care settings proposed (GP or ED) often involve a significant co-payment or waiting times.

Conclusion

Rescheduling codeine containing cold and flu preparations has been demonstrated to be unnecessary and unjustified given the lack of credible evidence to suggest this category of medication is being used inappropriately.

[redacted] is disappointed that the TGA Delegate has given no regard or inadequate regard to the NDPSC 2009 decision that deemed Schedule 2 and 3 appropriate for all the reasons detailed in our submission of the 7th May 2015. The Delegate has done very little to distinguish between codeine containing analgesics and codeine containing cold and flu. The reasons are very heavily weighted towards analgesic use, therefore **not applicable or relevant to cold and flu preparations**.

Codeine-containing cold and flu preparations continue to be different to codeine-containing analgesics; colds and flus are self-limiting and episodic. Patients treat their symptoms until such time as those symptoms are no longer bothersome at which point they cease taking the product. There is no potential for chronic use. Analgesics are different to cold and flu products. OTC analgesics are indicated for acute pain and, unfortunately, there is a small population that use the OTC analgesics for the treatment of chronic pain without medical supervision. Due to the differences in the way these different products, which are in different categories, are used, their associated risks should be considered independently of each other. Based on all the evidence, the risk benefit profile for codeine containing cold and flu preparations has not changed since the NDPSC decision in 2009, and we fail to see any evidence to suggest an increase of inappropriate use since 2010 for codeine containing analgesics, which is when these products were up-scheduled to Schedule 3

While [redacted] remains very vigilant regarding any new safety issues that may emerge for active ingredients, the variations in metabolism of codeine, in particular ultra-metabolisers who are at risk of morphine toxicity and adverse events, have not been concluded to be a high risk for **all** populations and **all** age groups. In fact the ACSOM remains undecided on this in line with other similar regulators. Effective labelling restrictions ensuring that the “at risk” populations are contraindicated, is a logical approach that has been successfully been adopted by other regulators with similar

regulatory standards as the TGA. Up-scheduling as the only appropriate measure is unjustified and unnecessary, when a range of feasible options have been presented that would successfully mitigate the perceived risks associated with codeine use. The proposed action is not appropriately adapted to the perceived problem.

Based on all the available material there is **no evidence** to suggest the risk/benefit profile of codeine containing cold and flu preparations has changed since the NDPSC decision made in 2009 therefore the current schedule 2 entry remains appropriate.

If despite the lack of evidence for this category the final decision remains unchanged, then a 2 year transition period should be permitted. This would allow sufficient time for [redacted] to revise the labelling and update the ARTG entries for impacted products. It is important to highlight that codeine containing cold and flu preparations are seasonal, with the height of sales in the winter months. To implement an effective date in the height of the cold and flu season after commitments are already locked in, especially for products containing pseudoephedrine which have permits associated with them, is illogical and will result in millions of dollars' worth of unnecessary write-offs. Given there is no immediate safety issue, a delayed implementation will allow [redacted] to exhaust products already in the supply chain and ensure a smooth transition for retailers and consumers.

Final Position

[redacted] requests that:

1. The Delegate reconsiders and sets aside the interim decision in relation to the scheduling of codeine for cold and flu preparations. The current scheduling remains appropriate and there should be no change to the entry in schedules 2 for codeine containing cold and flu preparations.
2. Failing request 1, [redacted] requests the Delegate defer the decision on the scheduling of codeine containing cold and flu preparations (Schedule 2) until such time robust evidence relating to abuse, misuse and dependency of codeine containing cold and flu preparations, pre and post the up-scheduling of codeine containing analgesics in 2010 has been presented and made available for public review, consultation and comment to ensure the precise intent of the scheduling item is made sufficiently clear.
3. Failing requests 1 & 2, [redacted] requests that an appropriate and manageable implementation time is granted. [redacted] requests consideration is given to a 2 year implementation i.e. November 2017.

[redacted]

[redacted]

[redacted]

CODEINE RESCHEDULING PROPOSAL

SUBMISSION FOR MARCH 2016 ACMS MEETING

Date: January 2016 Total number of pages: 4

[redacted]

1 INTRODUCTION

[redacted] welcomes the opportunity to comment on the consultation regarding the proposed amendments to the Poisons Standard, to be considered at the forthcoming ACMS Meeting in March 2016, as outlined in the Notice inviting public submissions under Reg 42ZCZK/42ZCZL of the Therapeutic Goods Regulations 1990. This document provides the Company response to the following scheduling proposal relating to codeine:

Schedule 3 (including, but not limited to codeine containing analgesics):

a. Proposal to amend the Schedule 3 entry to reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction; OR

b. Retain the interim decision to upschedule to Schedule 4.

As a diversified healthcare company [redacted] supplies a broad range of medicines and devices in Australia across the spectrum of prescription and non-prescription medicines. [redacted] is the Sponsor for several OTC analgesic products containing a combination of paracetamol and codeine. [redacted] strongly supports Quality Use of Medicines and a regulatory framework that ensures appropriate regulation commensurate with the potential risks to public health and safety. This is critical to ensure a viable medicines industry in line with the National Medicines Policy, to support continuing investment and innovation in Australia.

2 RESPONSE TO RESCHEDULING PROPOSAL FOR CODEINE

[redacted] fully supports adoption of **Option a**.

This approach aligns with that used successfully in the UK for many years based on introduction of a mandatory front of pack labelling statement in 2009 that specifies:

"Can cause addiction. Do not use for more than 3 days".

Option a will enable the vast majority of consumers who use codeine containing analgesics appropriately to continue to responsibly self-manage acute pain, including severe headaches and migraines which can be temporarily disabling. Timely access to pain relief is essential to allow individuals to continue their daily lives and remain within the workforce, contributing to the overall Australian economy,.

As outlined in our previous Company submission, [redacted] has supported the voluntary introduction of a prominent front of pack warning statement for OTC codeine containing analgesics and implemented pack changes accordingly. The warning ensures all consumers receive packs that clearly communicate the potential risks to enable them to differentiate between codeine containing analgesics and other pain relief products. [redacted] considers the proposal to reduce the pack size from 5 days to 3 days supply further strengthens the risk mitigation approach to minimise the potential for prolonged use that may lead to dependence.

For all Pharmacist Only (S3) medicines, pharmacists are required to assist the consumer with appropriate product selection, counsel on appropriate use and to recommend an alternative analgesic option where it is warranted. Since repeat purchases are a key factor in developing

dependence, [redacted] is also collaborating with the [redacted] and [redacted] to support implementation of MedsASSIST, a Real Time Monitoring (RTM) system for community pharmacies to assist in identifying consumers who are at risk of codeine dependence, facilitate access to education materials and support appropriate referral when required.

The system has the capacity for pharmacists to record clinical information and provide guidance regarding suitable referral pathways to support patients to better manage their pain and enhance health outcomes. The national rollout of the system is scheduled to commence in March 2016., with trials currently underway in approximately 150 pharmacies.

In addition to the above [redacted] supports the following additional measures:

- Full implementation, by the [redacted] and/or other pharmacy bodies, of a program based on the [redacted] '[redacted]' to equip pharmacists with the information they need to:
  - counsel and educate consumers about the appropriate use of codeine containing analgesics, including identification and management of medication overuse
  - educate and increase awareness of the management of chronic pain and accompanying mental health concerns such as anxiety and insomnia, which can also lead to problematic use.
- Improved collaboration between pharmacists, doctors and other services to assist people with these concerns, together with improved education for healthcare professionals and consumers
  - updating of the Product Information and Consumer Medicine Information to include information on the risk of addiction when the dose or recommended duration of use are exceeded to further mitigate risks of misuse.

As outlined in the previous Company submission [redacted] does not consider **Option b** to upschedule codeine containing analgesics to Schedule 4 (S4) as an appropriate way of minimising harm from misuse or dependence on the following grounds:

- The existing scheduling arrangements have not resulted in an increased trend in sales for OTC codeine containing analgesics or adverse reports linked to misuse or abuse.
- A Schedule 4 entry is no guarantee against misuse or abuse.
- Misuse and abuse of prescription opiate and psychoactive drugs has escalated significantly over the past several years.
- Unintended consequences of a change in scheduling may result in consumers receiving higher strengths and longer treatment durations than for products available over the counter.
- In the absence of the ability to monitor doctor-shopping, patients who have addiction and misuse problems are more likely to continue unnoticed until serious harm occurs.
- Restricting access by upscheduling will place a significant additional burden on the healthcare system if consumers have to visit a GP or emergency room for a prescription and increase costs for accessing pain medication.

- The majority of consumers who use codeine analgesics responsibly will no longer have timely access to pain relief that they have found to be highly effective, impacting their daily lives and ability to contribute in the work environment

3 RECOMMENDATION

- [redacted] supports **Option a** which will enhance Quality Use of Medicines through additional risk mitigation measures to ensure appropriate and responsible use of OTC products for short term, acute pain management including:
  - mandatory front of pack warnings *'Can cause addiction. Do not use for more than 3 days'*.
  - a reduction in pack size to a maximum of 3 days supply
  - implementation of MedsASSIST for community pharmacies to assist in identifying consumers who are at risk of codeine dependence, facilitate access to education materials and support appropriate referral when required

  [redacted] would be pleased to assist the ACMS with any further information that would inform the Committee discussions.

[redacted]

[redacted]

29 January 2016

The Secretary
Scheduling Secretariat
GPO Box 9848
Canberra ACT 2601
Email: Medicines.Scheduling@tga.gov.au

Cc: Department of Health

Dear Sir/Madam,

Notice inviting public submissions under Reg 42ZCZK of the Therapeutic Goods Regulations 1990 Scheduling proposals to be considered at the ACMS Meeting, March 2016

[redacted] welcomes the opportunity to provide public comment with relation to the scheduling proposal for **Schedule 3 codeine**.

[redacted] is a Medication Management Program designed to help patients take their medications safely, effectively and as prescribed by their doctor. [redacted] is free to patients and can be used as an Application on smartphones or tablet devices, and can also be accessed via web browser on computers.

[redacted] connects to pharmacy dispensing systems and automatically retrieves medication records to provide patients with visibility of their real time dispense information. It is also a powerful communication tool that can be used to send relevant educational messages to target patient groups.

[redacted] is an Australian software systems developer that listed on the ASX in late 2015 [redacted]. [redacted] is currently connected in over 1,400 community pharmacies across Australia and is integrated with all dispense systems. With over 115,000 registered patients using the program since launching in 2013, [redacted].

Codeine

[redacted] supports the position taken by a number of key stakeholders to maintain combination codeine analgesics as Schedule 3.

[redacted] recognises the safety concerns relating to the overuse of Schedule 3 codeine analgesics, however [redacted] believes effective strategies can be implemented to minimise potential for overuse and patient harm without disadvantaging the vast majority of consumers who use these

medications appropriately or placing excessive pressures on GPs and the healthcare system should these medications be rescheduled to Schedule 4.

A shared recommendation amongst the key stakeholders such as the [redacted], [redacted] and the [redacted] is for the implementation of a nationwide **real time recording and reporting system.** The system would enable pharmacists and prescribers to easily identify patients who are taking excessive quantities of Schedule 3 codeine analgesics, and make informed clinical decisions for the appropriate management of these patients

Whilst IT tools which facilitate real time recording and reporting can greatly assist prescribers and pharmacists in controlling the supply of medications, [redacted] believes it is imperative to have the patient central to any workable solution, giving them necessary information that is both timely and relevant. [redacted] believes that patient information delivered via mobile device or web browser provides the greatest opportunity of influencing behaviour, and [redacted] is ready and able to provide a solution which can be implemented immediately on a national scale.

Recommendation

Schedule 3 (including, but not limited to codeine containing analgesics)

1) [redacted] supports the option to **amend the Schedule 3 entry to reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction.**

2) [redacted] supports a holistic solution for minimising medication overuse which must place patients at the centre. This should include a **patient education program** which highlights the risks associated with excessive use of these medications.

3) [redacted] recommends **Schedule 3 codeine should be dispensed via the community pharmacy dispense systems**. This will allow pharmacists to review patient history prior to supply. [redacted] believes this will greatly support pharmacists to promote the safe and effective use of Schedule 3 codeine.

4) [redacted] recommends that any **real time recording and reporting system** should integrate seamlessly with all community pharmacy dispense systems, capture all medications subject to overuse including Schedule 3 codeine, and allow dispense information to be shared across community pharmacies.

[redacted] Patient Pain Education Program

Addiction cycles often begin with unintended overuse of Schedule 3 codeine analgesics. This is supported by a recent study in The Medical Journal of Australia which showed that accidental overdoses were more common (48.8%) than intentional deaths (34.7%)[1].

Roxburgh et al concluded that given the readily available nature of over-the-counter codeine, education about the dangers of taking too much codeine is needed[1].

[1] Roxburgh A, Hall WD, Burns L, Pilgrim J, Saar E, Nielsen S, Degenhardt L, Trends and characteristics of accidental and intentional codeine overdose deaths in Australia, The Medical Journal of Australia, 2015; 203 (7): 299.

[redacted] has recently launched a **Patient Pain Education Program** in Victoria in partnership with [redacted] which aims to improve the quality use of medicines by delivering educational messages directly to patients via smartphone, tablet or web browser.

Patients are educated on the safe and effective use of Schedule 3 codeine analgesics, thereby reducing the risk of addiction and serious side effects. The messages also highlight the risks of long term use, signs of addiction and provide general pain management advice including referral pathways. Providing this information electronically allows information to be customised to the patient and delivered in an engaging and interactive manner compared with traditional methods such as patient brochures.

How [redacted] Patient Pain Education Program works

Patient requests for a Schedule 3 codeine analgesic at the community pharmacy:

1. The medication will be dispensed via the community pharmacy dispense system.
2. The patient will be asked to join [redacted]
3. The patient's profile on [redacted] will be updated with a record of their dispensed codeine medication, thereby providing patients with full visibility of their supply and usage.
4. The [redacted] system will send a series of messages to the patient that reinforce information provided by the pharmacist about the safe and effective use of these medications.

Content of Messages

There are 3 messages in the series which are sent to patients at different times depending on their usage levels (Refer to Appendix A):

1. Upon initiation: *"Taking Your Codeine Pain Reliever Safely"*
2. When patient has >2 dispensed per fortnight: *"Dangers of Codeine Overuse"*
3. When patient has >4 dispensed per month: "*Signs of Codeine Addiction"*

By proactively delivering education to patients at the time they are using these medications, patients are empowered to make more informed decisions about their own health. Healthcare professionals may not be aware of a patient's addiction to Schedule 3 codeine, or may find conversations about suspected addiction difficult to initiate. [redacted] can assist patients to identify their own addiction and encourage them to speak with their healthcare professional.

In the future, the [redacted] Patient Education Program can be expanded to include any medication which is subject to overuse including benzodiazepines and prescription pain medication.

[redacted] Monitoring - a real time recording and reporting system

A recent study published in The Medical Journal of Australia showed the overall rate of codeine-related deaths increased from 3.5 per million in 2000 to 8.7 per million in 2009, however only 7.8% were specifically attributed to codeine toxicity while 83.7% of these deaths were a result of multiple drug toxicity[1]. Therefore, [redacted] firmly believes a real time recording and reporting system must capture all medications subject to overuse, including (but not limited to):

- Schedule 3 codeine
- Schedule 3 pseudoephedrine
- Schedule 4 & Schedule 8 prescription pain medications
- Schedule 4 & Schedule 8 benzodiazepines

[redacted] does not support a real time recording and reporting system which can only capture Schedule 3 codeine, as this is will unlikely lead to any significant reduction of harm for the patient.

[redacted] is able to capture real time dispense data for all medications at [redacted] enabled pharmacies and can, where appropriate and following privacy legislation, share visibility of dispenses across pharmacies. Therefore [redacted] can offer an effective and immediate solution for real time monitoring for Schedule 3 codeine and other medications subject to overuse.

[redacted] **Monitoring** will be an integrated system that can also work on a standalone basis for the purpose of a real time reporting and recording system. Therefore a pharmacy does not need to adopt the full version of [redacted] which also includes the Patient Medication Management Program unless they want to provide patient information via [redacted] Patients with existing [redacted] profiles are automatically identified in the [redacted] Monitoring system.

How [redacted] Monitoring works

Patient requests for Schedule 3 codeine **or** presents with a valid prescription for any other medication subject to overuse at the pharmacy:

1) Patient is registered to [redacted] (if not already registered). The [redacted] Monitoring System will use Medicare Card details to create a unique identifier for the patient.
2) Pharmacist to review patient history in the [redacted] Monitoring System to determine whether supply is appropriate.
3) If supply is appropriate, pharmacist to dispense the medication using the pharmacy dispense software. Information is automatically captured in [redacted]
4) If supply is not appropriate, pharmacist should indicate in [redacted] Monitoring that supply was refused. Pharmacist can create notes and log interactions with the patient.

If the pharmacy is subscribed to the full version of [redacted] patients who wish to access their personal dispense records and receive medication information can register free for [redacted] on smart phone, tablet or computer using a unique Activation Code provided by the pharmacist.

In order for [redacted] to fulfil the requirements of a national real time recording and reporting system:

- All pharmacies must be connected with [redacted] Monitoring.
- All patients supplied with medication subject to overuse must be registered with [redacted]
- All Schedule 3 codeine supplied to patients must be dispensed.

[redacted] acknowledges this will require changes to the current legislative framework, however [redacted] believes this system can provide an effective and immediate solution for real time recording and reporting of medications subject to overuse.

Over the next 6 months, [redacted] will integrate with prescribing software. This will enable prescribers to view real time dispense information, which can further facilitate clinical decision making and improved patient health outcomes.

Summary

[redacted] appreciates the opportunity to provide public comment on the proposed amendments to the scheduling of Schedule 3 codeine. [redacted] strongly believes an effective solution for codeine risk reduction must be holistic and include the patient at the centre. Implementation of a **patient education program** and **real time recording and reporting system**, in addition to reduction in pack size and labelling of products to warn of addiction, will support the safe and effective use of Schedule 3 codeine without the need to reschedule to Schedule 4.

[redacted] currently operates Australia wide in over 1,400 pharmacies with over 115,000 active users. [redacted] is already delivering a patient education program for Schedule 3 codeine and can provide an effective and immediate solution for a real time recording and reporting system. MedAdvisor would welcome the opportunity to be involved in these codeine risk reduction strategies.

[redacted]

[redacted]