From: [redacted]
To: Medicines Scheduling
Cc: Farrer@aph.gov.au
Subject: Codeine rescheduling
Date: [redacted]

The overwhelming majority of codeine users treat codeine with proper regard to its potential side effects, paying proper attention to dosage and length of use. To reschedule codeine to a prescription medication would greatly inconvenience all patients and come at an enormous cost to patients and the government and in my opinion would provide no greater safeguard to patient health.

Recently two sportsmen had a misadventure with a S8 medication obtained on prescription , I believe.

Of the reported 153 patients whose deaths were reported to be " linked" to codeine use in the last 10 years, half were using the drug recreationally, reportedly, and most of the rest were accidental.

This a miniscule number of patients, most of whom deliberately misused the drug or had little regard for the labelled or spoken advice. These numbers are unlikely to change if codeine were a prescription medication. And let us not forget that a person's health is primarily his or her own responsibilty, not that of the doctor, who is just a service provider.

I believe that better outcomes would be possible if the drug were moved to S3 requiring a pharmacist to make the sale or as I prefer to view it , the pharmacist prescription.

This brings me to another point namely government licensed prescribing pharmacists. Those pharmacists interested in becoming independent prescribers could be prepared in the final 2 years of their university course to use their superior knowledge of pharmacology for the purpose of prescribing, by rearrangement of the course material. Already qualified pharmacists could attend part-time courses to reorient their skills over say a 3-6 month period. This pharmacist would be remunerated by the government and have no ties to a pharmacy.

Obviously a higher remuneration would be expected by those choosing to take on this extra resposibilty but the costs would be more than covered by the reduction in forced visits to the doctor especially for repeat scripts for ongoing medication. I believe that most of the regular 3-6 monthly visits for repeat scripts are unnecessary but are the gravy on the doctors gravy train. A visit to an independent prescribing pharmacist every 2 years would be more than adequate between prescriptions but a voluntary visit to the doctor could take place at the patient's wish at any time.

Studies in Europe have concluded that it is in the patient's best interest to separate the functions of diagnosis and prescribing with 2 individuals, one for each function, thus providing transparency, with the diagnostician printing out and signing, ie. owning, the diagnosis, this to be given to the patient who will present it to whichever health practitioner is deemed the most suitable.

Some patients are prescribed the wrong drug by the doctor and the mistake goes undetected for many years until a chance conversation with a pharmacist reveals the error. Separation of the two functions would prevent this.

Not all ailments need a doctor's diagnosis. Some are previously diagnosed, some are simply diagnosed, at least in the first instance.

The savings in healthcare costs to the community would be enormous, allowing other health care regimes to be subsidised by the government and the potential to encourage far healthier lifestyles would increase since the doctor's role would change from allowing access to drugs to one of advising a healthy lifestyle. The extremely expensive and ineffectual conveyor belt approach to healthcare would cease.

[redacted]

From: [redacted]
To: Medicines Scheduling
Subject: Codeine containing product up-scheduling
Date: [redacted]

To whom it may concern,

As a pharmacist I am concerning about the up-scheduling of the many codeine-containing products that the TGA is proposing due to many, many un-sounded reasons:

1. The cost of living of our people is higher, increase unemployment rate and other retail sectors will suffer even more.

   A customer has to pay an up-front fees of about $50-$70 to see a doctor plus they have to pay a higher price to purchase a codeine-containing product which may cost up to $20-$30. The total is about $100! They may not even want to waste time and to spend that much money. Yet, this may mean that the system has denied them of an efficient way to get to the appropriate and timely treatment. The other way around is that they keep on going from one doctor to the next (doctor shopping) and ended up not going to work, and the result is higher unemployment rate to feed their habit. Then our nation is in more debt and the government will keep on taking more and more money from the pharmacy and other sectors.

2. The waste of resource if patient has to only see Doctors for only codeine based product.

   Doctors are currently stressed with the work-load and to add to this stress, there are now more customers waiting to just see a doctor for a script of, say, [redacted]. This does not taken into account of customers who are doctor-shopping. If they do, this will only make the waiting time at the doctor getting worse.

3. Possibility of toxicity due to combination or over use of opioids. Deaths may result more rather than less.

   A customer may think that since they are seeing the doctor for a script of codeine-containing product, they might say that their pain is not totally managed by just the item requested. They would like to have something in conjunction with it or a tramadol in case they need it. Toxicity can result due to interactions and due to doctor shopping. This may lead to more deaths than anticipated otherwise.

4. Lost of viable time or productivity when customer wait to see a Doctor.

   The time to sit and wait at a doctor is more useful if they are able to purchase the pain medication in a timely manner and get back to work.

5. Only minority of people using it wrongly. We can monitor such frequent purchase by a system similar to Project Stop.

   Just because of a few minority who uses the medication wrongly doesn't mean that everyone has to be punished for it. Most people has a debilitating pain and to be able to purchase the medication when they needed, at the right time, save them a lot of hassle and they can go back and being productive.

Above are only a few of the many more reasons that I sincerely hope the TGA should think again carefully of their decision to up-scheduling codeine-containing products. It will not do any good for the nation but the reverse will bound to be happen. Pharmacists are

capable of advising, counseling and monitoring the usage of those products given that they are trained for that many years. In any system, any condition, there are always pros and cons. Even when the TGA thinks “seeing the doctors will prevent mis-use” yet this will prompt them to doctor-shopping more and will create a new “disease” for the nation. In my opinion, the TGA has over-regulated this one.

Sincerely,

[redacted]

[redacted]

SUBMISSION RE CHANGES TO SCHEDULING OF PRODUCTS CONTAINING CODEINE

14th October 2015

The changes to Scheduling of Codeine products will make no change to the abuse of Codeine.

We have patients who have scripts written out by a Doctor for 240 Panadeine Forte tablets at a time , this is a total of 7,200mg of Codeine supplied on the orders of a Doctor. The Government has full details of these scripts via Medicare and Medicare online , they know who prescribed it, who dispensed it and how many times the patient has collected it and how many different Doctors and Pharmacies the patient has visited. However they choose to ignore this information , when it could be used to prevent abuse of large quantities of Codeine. They already have the information but do not act on it.

When a retail Pharmacist sells a packet of 24 Panadeine tablets , it contains a total of 192mg of Codeine. How can forcing the patient to obtain a Prescription for the packet of Panadeine prevent abuse of Codeine.

We are a country Pharmacy and our patients wait about 10 days for a Doctors appointment and we have had days recently where we had No Doctors for consecutive days while our Doctors were away.

Our patients safely use a wide range of Codeine containing products for pain control and Coughs and Colds. They are found in products for Arthritis, Migraine,Headache, Flu, Cough, etc

If these products become script only our patients will have to wait 10 days to obtain a prescription or obtain a Doctors appointment else where if possible and drive for 2 to 3 hours return to get to [redacted] or [redacted].

But once the Doctors are wasting their time on this pointless exercise of prescribing over the counter medicines the waiting time will no doubt increase.

So commonsense says this change is not only pointless, but will cause extreme pain and anxiety and needless expense to a large number of patients who would never abuse Codeine. So because a very small number of patients abuse Codeine we will punish the majority of people who do not abuse Codeine.

The Health System is always screaming out about the lack of funding. Rescheduling Codeine will be one of the most expensive farces in the History of Australia. The Government will be paying Doctors a standard consulting fee for writing a Prescription for a Packet of painkillers or a Cold and Flu tablet.

So a transaction that cost the Government nothing will now cost them between $20-00 to $40-00 for the patient to obtain a prescription from a Doctor and then the cost to have the script made up at the Pharmacy.

The super clinics will be rubbing their hands together for this one, money for jam.

Just think for a moment how many products containing Codeine are sold each day with no ill effects and then think how much it is going to cost the taxpayer to fund this pointless exercise.

If the people behind this really want to improve the Health of the population , why not start changing the rules for a drug that does far more damage such as Alcohol or Nicotine or actually deal with the abuse of Codeine that is occurring via prescriptions, doctor shopping , pharmacy shopping and all subsidised by the Government.

Please put yourself in my customers shoes. You are in pain or suffering from cold and flu symptoms and you walk into a Pharmacy to get instant relief with products that you know will work for you, but you are told to get a prescription and you will have to wait at least 10 days for that or start driving to another Doctor over 100 kilometers away(assuming you have access to a car). Remember in country areas we have no public transport and very very few doctors.

The most practical solution is a real time monitoring tool to help identify the minority of patients who are misusing or abusing Codeine. Up scheduling won't solve the issue , Oxycontin is in the highest Schedule but without real time monitoring Doctors and Pharmacists are unable to identify potential Pharmacy or Doctor Shopping by patients.

Please realize the Hardship and Inconvenience this will cause to the rural community and think carefully before you act.

Above all use common sense..

Yours sincerely

[redacted]

From: [redacted]
To: Medicines Scheduling
Subject: Rescheduling of Codeine
Date: [redacted]

Thanks for the opportunity to comment further on the proposal to support rescheduling of CCA to schedule 4.

To avoid any doubt, I would strongly support this change, from the perspective of a physician and addictions medicine specialist.

I saw a patient last week who presented for treatment of [redacted] opioid use disorder because she became aware of the proposed rescheduling of codeine.
I discussed this issue with [redacted] and found [redacted] was very strongly in support of the proposed change. [redacted] was happy for me to share [redacted] history with the TGA.
Now aged [redacted] first was exposed to CCA at [redacted] when [redacted] GP recommended 1 'Mersyndol' tablet for [redacted]. Two years later [redacted]e was taking [redacted] tablets daily.
This number gradually increased, to the point that [redacted] was taking [redacted] Mersyndol tablets daily when [redacted] presented, (~$6-$10 per day per pack of 40, depending on the pharmacy).
[redacted] has been careful about the frequency of pharmacy visits, and tracks [redacted] use of individual pharmacies to ensure [redacted] does not present too frequently.

On only one occasion has a pharmacist decline to sell [redacted] the product.

A situation where a patient loses control over their use of CCA, and takes 18gm or more of paracetamol (4.5 x the recommended daily maximum dose of paracetamol) daily on a long term basis should not be facilitated by the ready access to these products. This patient was strongly in support of this move, which might have prevented [redacted] developing an opioid use disorder in the first place.

The efficacy of CCA is very limited as is clearly laid out in the statement of reasons, and mainly due to the other compound not the codeine..
This patient may or may not be an ultra rapid metaboliser; while this is of theoretical interest and may help explain the increase in use and harms from CCAs (though I have not found any studies which examine the 2D6 activity in those who have developed opioid dependence on codeine) it does not really affect those who develop dependence.

There are effective alternative analgesics available, as shown by the Oxford Pain Group where number needed to treat is smallest for anti-inflammatories (from 2-4) and as high as 16 for codeine solo.
I consider the arguments put against this move are specious and unfounded. We have clear evidence of real harms (not least 573 deaths from codeine between 2007 and 2011 as recently reported in MJA).
I commend the committee for its bold stance and clear reasons. Please hold firm against the narrow economic arguments of pharmacies and CCA manufacturers.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] be

[redacted]

[redacted]

The Therapeutic Goods Administration

To whom it may concern:

SUBJECT: Pending decision by TGA to make painkillers containing Codeine available on prescription only.

I write this letter **strongly protesting** the TGA's pending decision to make all medicines including painkillers containing Codeine and currently available over the counter to be available on prescription only.

I have no doubt that this initiative is being pushed by the AMA for the benefit of the AMA in some way shape or form. The reasons being proffered by the AMA is that there is an increase in the abuse of and deaths relating to medicines containing Codeine. The AMA also claims that Codeine is addictive and dangerous if used over a long period of time. Paracetamol if used in large quantities for long periods is also very dangerous. In fact any substance no matter how benign can be detrimental to health if taken in large enough quantities over an extended period. This would include vitamin tablets and supplements which are rammed down our throats all day everyday in advertising.

At [redacted] years of age I use painkillers containing Codeine to obtain some relief from [redacted] pain in [redacted] The painkillers I use contain 500mg of Paracetamol and 8mg of Codeine, not a significant amount of Codeine. Typically I use common name painkillers such as [redacted]

As a long time objector to taking any form of medicines I do find that taking these painkillers for the purpose stated I gain relief from pain and therefore a better quality of life. These painkillers were recommended on advice of my doctor. I use them judiciously and only when required. The use of straight Paracetamol for joint pain is about as effective as eating smarties. It is acknowledged in medical circles that Paracetamol is ineffective for back pain. Due to an pre-existing [redacted] problem my doctor does not recommend anti inflammatory medication for [redacted] pain.

Such painkillers are presently reasonably cheap but if the TGA goes ahead with banning them over the counter this will not only increase the price of the medicine but cause me added time and expense by having to seek out my doctor whenever I have pain. When pain strikes I want pain relief **now** not tomorrow or next week when I am able to get an appointment to see my doctor. Not only will it affect me personally both financially and physically but also many hundreds of thousands of people in the same position as me who are probably mostly older people. Most of these people are responsible and have held important and responsible positions throughout their working lives. They have contributed to the growth and economic welfare of this country yet suddenly the TGA seemingly regards them as irresponsible and should be treated like children. I regard my self as responsible and am aware of the potential dangers of taking large amounts of **any** medicine for extended periods. Just because I have been fortunate enough to reach [redacted] years of age does not mean I have suddenly surrendered by senses and become demented and not able to make decisions about what I will or will not put into my body. I have never been drug addict and am not likely to start now.

The AMA's argument that such medicines have caused greater addiction, abuse and deaths fails miserably when we look at other substances that are freely available and in fact promoted vigorously to the public which includes children. Take for example soft drinks, sweets and fast food. The abuse of these foods can lead to addiction, being overweight which can lead to all manner of health problems such as heart disease, diabetes and even death. In fact overweight, heart problems and diabetes caused through excessive consumption and drinking these foods is an acknowledged world wide epidemic. This has created a huge burden on the health budget in this country. Is the AMA advocating that people should only be permitted to buy these foods on prescription?

Alcohol has long be known as an addictive substance. It can lead to misery, breakdown of families, crime and death. Does the AMA advocate alcohol be available only on prescription?

Tobacco, we all know what damage tobacco does to the health yet it is legal and it is available on request by people over the legal age. Does the AMA advocate tobacco be available only on prescription.

Sports power drinks containing large amounts of caffeine are freely available everywhere to all and sundry even children. Caffeine is an addictive substance and can cause health problems and even death. Does the AMA advocate these being available on prescription? I could go on and on about the many harmful substances that are freely available and not required to have a prescription but I am sure you get my message.

It is always the same old story where the abuse of something by a minority group spoils it for the majority who do the right thing and have to suffer. An example, speed and red light cameras. If it wasn't for the actions of the minority of drivers who have no regard for the road rules and who cause mayhem on our roads then the rest of the motoring public would not be subjected to those big brother speed and red light cameras and continued harassment by traffic authorities.

Good governments don't intrude or interfere with the everyday lives of their citizens and neither they should. This initiative to prevent the purchase of Codeine medicines smacks of big brother. We the citizens of this country want less regulation and interference from big government.

People will always find a way to abuse substances whether such substances are restricted, legal or illegal. They will continue to obtain what they want by committing crime or doctor shopping or whatever. The drug ICE is a drug of choice at the moment but is the AMA advocating that ICE should be only available on prescription.

Give the many hundreds of thousands of responsible people who now use painkillers containing small amounts of Codeine a bit of credit and allow them to be the arbiters of what they do with their body in regards to pain relief. Don't make the obtaining and use of such painkillers an expensive, laborious and unworkable exercise particularly for people who have limited incomes or means to get to see a doctor when they need pain relief. At my age time is precious and I don't intend to sit around in a doctor's surgery waiting to see the doctor for some pain relief.

I do however agree that painkillers or medicines containing large amounts of Codeine or synthetic opioid, e.g. [redacted] etc should only be available on prescription.

I urge the TGA not to lump everyone into the incompetent basket and not restrict those medicines that have small amounts of Codeine such as [redacted] and the like.

[redacted]

From: TGA Info
To: [redacted]
Subject: RE: New feedback received for Chronic Disease [SEC=UNCLASSIFIED]
Date: Wednesday, 14 October 2015 3:58:33 PM

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]
Regulatory Services and Improvement Branch

Phone: 1800 020 653 Fax: 02 6203 1605
Email: info@tga.gov.au

Therapeutic Goods Administration
Department of Health
PO Box 100
Woden ACT 2606 Australia
www.tga.gov.au

From: [redacted]
Sent: [redacted]
To: PHSD FRONTDESK
Subject: New feedback received for Chronic Disease

[redacted]

FEEDBACKTYPE: ChronicDisease

[redacted]

[redacted]

ENQUIRYCOMMENTS: Regarding codeine -- I have been using codeine as a pain reliever ([redacted]) ever since my doctor told me several years ago that that was better than things that can upset the stomach. I do not use aspirin as I have [redacted]. Always -- and especially recently -- the pharmacist reminds me to only take 8 capsules a day. there is no way I would forget and take too much. I hate the thought of having to go to the doctor constantly for a script, it is not necessary.

[redacted]

[redacted]

[redacted]

14th October 2015

The Secretary, Advisory Committee on Medicines Scheduling

SUBMISSION: Proposed Amendments to the Poisons Standard (Medicines) – scheduling of codeine

I am writing on behalf of the [redacted] – a network of 225 franchised pharmacies across Australia – to formally outline our opposition to the proposed scheduling change of codeine.

At the outset, I want to state that we acknowledge the misuse of codeine is a serious and growing concern and – as health professionals – we are committed to helping to address this problem. However, we do NOT believe up-scheduling codeine to a prescription-only medicine will resolve this problem.

1.0 About [redacted]

[redacted] employs more than 5,000 people across our national network of franchised pharmacies, including 750 pharmacists. We are the leading health-focused community pharmacy network and take great pride in our value health offering.

As pharmacists, we value the important and growing role we play in providing accessible health care advice to community members. This is why we have increased the health services we deliver through our pharmacies from vaccination, complex medication management, medication adherence programs, cardiovascular risk monitoring, diabetes support, hearing and bowel cancer screenings to mention a few.

While difficult to document, without these services (many free) to the community, including pain management / codeine use counselling, the cost of escalation of chronic disease and increased hospital admissions cannot surely be ignored.

2.0 The role of pharmacists

Pharmacists are medication experts who maintain their expertise through continued professional education and training. They play a fundamental and active role in assisting consumers to appropriately manage their pain through advice (in conjunction with other members of the health care team) and the provision of over-the-counter analgesics (in accordance with the Quality Use of Medicines principles), prescription medication and other treatments.

Pharmacists provide customers with information about the effective and appropriate use of all medications – including over-the-counter analgesic products – and any potential side effects and risks of harm. As such, they use their professional judgement to prevent the supply of medicines to consumers with the potential for drug abuse or dependency and to educate the broader community on the dangers of drug misuse.

[redacted]

[redacted]

Additionally, pharmacists are required by law to determine whether it is appropriate to supply over-the-counter medications containing codeine to consumers.

This proposed change disregards the expertise of pharmacists – who are trained health professionals - and the important and growing role they play in the frontline delivery of primary care and improved health literacy.

Pharmacists need relevant information from patients to ensure they can give appropriate advice and help select the right product (if a product is necessary). Currently, the vast majority of patients who misuse codeine through a dangerous level of consumption do not disclose their consumption levels to the pharmacist, or any other health professional. The anecdotal stories of patients taking more than 60 [redacted] tables per day indicates that they are purchasing three packets each day. There is absolutely no evidence that these patients are purchasing multiple packs from an individual pharmacy. These patients are pharmacy 'hopping'. Only a real-time recording and reporting system would identify these patients and help address this issue. It is important to note that if these patients are visiting multiple doctors to procure multiple packs of [redacted] with much higher levels of codeine, there is also no monitoring of the product across the health system.

3.0 Concerns with the proposed scheduling change

Terry White Group's concerns with the Scheduling Committee's proposed change fall into three distinct categories:

- Genuine user impacts – price and convenience
- Increased Medicare and Pharmaceutical Benefits Scheme (PBS) costs, and
- Failure to address the cause of the problem.

3.1 Genuine user impacts

We strongly believe that the great majority of Australians who use medicines containing codeine act responsibly and follow the advice of their health professionals. They use these products because they want a safe, affordable, effective and convenient solution to deal with intermittent, moderate pain. Mandating the need for a prescription for the purchase of, for example, a cold and flu tablet containing 10mg of codeine, penalises this great majority of genuine and responsible users.

The impact of this proposed change on these genuine users will almost certainly mean pain relief medications will be more expensive to purchase and more difficult to obtain. Access will also be an issue because there are many locations across Australia where [redacted] Chemists operate after hours and there is no accessible doctor, except call out doctor services or accident and emergency centres. Requiring consumers to see a doctor will increase costs to patients who do not have access to bulk billing practices and also likely increase the overall wait period for all patients to see a GP.

In addition to the potential cost and inconvenience, associated with seeing a GP, we believe some pain medications currently available over-the-counter could triple in price across the industry if they become prescription-only medicines.

3.2 Increased Medicare and PBS costs

With Medicare now being billed more than one million times a day, a move to force responsible consumers to see a doctor for a prescription for codeine medicines will inevitably result in increased

[redacted]

[redacted]

Medicare and PBS costs. This is particularly the case if doctors elect to prescribe codeine as per the appropriate protocols and do so with prescriptions for one primary pack, which will only last for a few days of therapy.

If the doctor writes multiple repeat prescriptions this defeats the very purpose of the proposed measure, as those who misuse the products will visit pharmacies every few days for a repeat prescription. We also expect some doctors will prescribe consumers high strength pain therapy, including opioids listed on the PBS. Pensioners in particular will demand items on the PBS. In addition to increasing the workload of doctors, up-scheduling codeine is also likely to create greater inefficiencies in an already very strained primary health care system.

3.3 Failure to address the cause of the problem

The most significant concern we have with this proposed solution is that it does NOT address the cause of a growing and serious problem. Mandating for codeine products to be prescription-only will not stop misuse or abuse. This is the case for many prescription-only medications, including Schedule 4 and Schedule 8 opioid analgesics, which are also associated with inappropriate misuse and abuse. Additionally, there are no mechanisms in place for monitoring prescription-based Schedule 4 purchases – which is a key component of the sophisticated response we recommend to address the complex problem of codeine abuse.

Almost every patient misusing codeine is fully aware that they are consuming amounts in excess of recommended doses, often going to great lengths to hide this fact from their health professionals. They will, therefore, continue to work around the system and simply 'doctor shop'. This is why we believe a comprehensive, coordinated series of initiatives should be implemented aimed at monitoring and stopping at-risk consumers from purchasing medication containing codeine and educating the community about the potential for addiction. These initiatives are detailed in section 4.0 – proposed solution.

4.0 Proposed solution

[redacted] supports the Pharmacy Guild's alternative to this proposal, which includes:

- A real-time recording and reporting system to identify consumers potentially at-risk and prevent medication misuse be introduced in every Australian State and Territory. A prototype of such a system (the Electronic Reporting of Controlled Drugs system) has already been developed, with cross industry and consumer support. This system would allow doctors and pharmacists to monitor in real time, the prescribing and dispensing of a range of medicines with the potential for misuse and harm. This allows these health professionals to identify at-risk consumers, facilitate access to education materials and support appropriate referral when required.

  We note that the Australian Medical Association (AMA); Consumers Health Forum of Australia (CHF); Medical Software Industry Association (MSIA); Pharmaceutical Society of Australia; The Pharmacy Guild of Australia; The Royal Australian College of General Practitioners (RACGP); The Royal Australasian College of Physicians (RACP); and The Society of Hospital Pharmacists of Australia (SHPA) have written to the Federal Health Ministers and all State and Territory Health

[redacted]

[redacted]

Ministers pointing out that coroners in jurisdictions around Australia have repeatedly called for the urgent implementation of a real-time prescription monitoring system.

We appreciate that the Scheduling Committee does not have the authority to mandate the national implementation of a real-time system like ERRCD. However, we think this is a critical component of the holistic solution required to address this complex problem. As such, we have written to the Federal Health Minister and all State and Territory Health Ministers urging them to take urgent action to introduce a real-time recording and reporting system to identify, and support, potentially at-risk consumers.

- A mandatory front-of-pack warning about the potential for addiction.

We also believe consideration should be given to improved recording requirements to enable monitoring of codeine dispensing (as is the case for pseudoephedrine). As a leading health-focused community pharmacy network, we fully support such a move and would be in a position to quickly implement this change across our franchised stores. Again, we appreciate that this is outside the authority of the Scheduling Committee and have referenced this recommendation in our engagement with Federal, State and Territory Health Ministers.

Thank you for giving this matter the serious consideration it deserves. Please do not hesitate to call me if you wish to clarify any matters contained in this submission.

Yours sincerely

[redacted]

[redacted]

From: [redacted]
[redacted]
Cc: [redacted]
Subject: Codeine on Prescription
Date: [redacted]

To whom it may concern,

I am writing to you in regards to codeine containing products that are issued over the counter at pharmacies.

I have heard that there is a proposal to change the dispensing of this medication by requiring a prescription.

I am a severe [redacted] sufferer who uses codeine containing medications to ease my constant pain. I am also on [redacted] preventative medication but need pain medication to help with my symptoms. The only pain medication that works for me is those containing codeine.

I am all for monitoring this type of medication and often provide ID to pharmacies.

There is no way I can continually go to my GP to get a script, especially when I try to work full time and when I have run out of pills after GP hours and are in desperate need of pain relief.

There must be a better way of monitoring this. It is unfair to punish the people who use it correctly for the minority of individuals who abuse it.

Please take this in to consideration on behalf of all the migraine sufferers out there. This is a debilitating condition and now you are going to make it even more difficult for us.

Thanks for listening.

[redacted]

A [redacted] of [redacted] years.

[redacted]

[redacted]

[redacted]

[redacted]

A submission by a member of the public to the Therapeutic Goods Administration.

On the Rescheduling of OTC Codeine containing medicines to Schedule 4, in response to the Interim decisions on matters referred to an expert advisory committee (1.1),

Scheduling proposals referred to the August 2015 meeting of the Advisory Committee on Medicines Scheduling (ACMS #15) Of 1 October 2015

1.1 Codeine

Thank you for the opportunity to comment on the proposal. I apologise for the poor quality of the presentation but I lack the time to bring it up to standard.

Executive Summary

The major concern before the committee is the harm that is caused by OTC codeine preparations when abused.

The proposal presented below:

- addresses this concern by identifying individuals 'at-risk' and preventing supply to them without prescription,
- allows pharmacies to supply OTC only to customers who are not at risk,
- identifying individuals whose past usage indicates they are in danger of transitioning to 'at-risk' thereby allowing early intervention to prevent transitions occurring,
- collects data on both OTC and prescription events for transmission to Medicare, all traced to the purchasers Medicare Card,
- provides a database of usage against individual Medicare Cards for population wide research at both a data mining level and down to individual patients.

Unlike the current proposal before the committee, this model does not impose additional strain on the GP system. It will require both legislative and system changes, neither of which should be onerous either financially or politically.

It would likely be supported even by occasional OTC users who might welcome improved information on pain relief and a better relationship with medical authorities.

Medical researchers would have vastly improved information on codeine use and would have candidate lists to precisely target surveys of users (and non-users) of differing usage patterns.

This model can only be implemented because of the conditions that currently occur in Australia and in practically no other country. Once OTC preparations are moved to Schedule 4, the world may never again have the opportunity to conduct an epidemiology study into drugs of addiction of this magnitude ever again. And public health would be worse off for it.

Submission Format

My submission is in two parts:

Part 1: A suggestion on a better approach to dealing with the problem, and

Part 2: My experiences with OTC codeine-containing analgesics.

Part 1: A Unique Opportunity.

The Proposal.

I suggest we introduce a new type of product class, one that requires pharmacy outlets to sell OTC preparations of codeine containing medications only on presentation of a Medicare card and only after verification against a (new) database maintained by Medicare of 'at risk' individuals.

Further, in purchasing OTC codeine products the customer agrees to supply their Medicare details for verification of at-risk status and to allow the recording of the supply of the medicine for clinical and epidemiological research. Customers must also accept that if clinical intervention is deemed warranted then future supply of the medicines OTC will be dependent on undertaking actions as directed by the relevant authority.

Main Process

When a customer requests an OTC codeine product, the pharmacy:

1. checks with Medicare that there are no supply restrictions on this individual and then
2. supplies the item, then
3. the details of the transaction, including number supplied and the customer's Medicare id is forwarded to Medicare and stored against the customer's history.

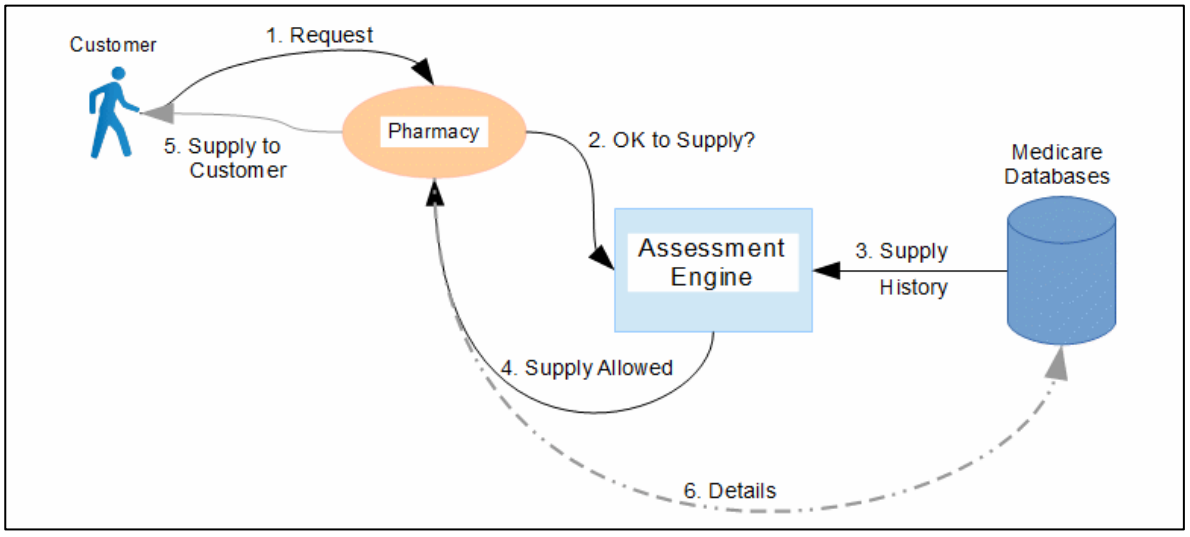

Figure 1. Main Process – OTC Supply with No Conditions plus Recording of Details of Supply (for patients not at risk)

As supply of OTC codeine is a privilege not a right, it might even be acceptable to have customers maintain a diary of use, principally date, dose and condition. Data volume problems would restrict this to a sample of users but would still collect a lot of very reliable data to understand how these drugs are used.

Alternate Processes 1

If at step 1 the individual's history shows an at-risk status:

1. the pharmacy is instructed not to supply, and
2. instructed to advise the customer of what actions they should take (such as calling the relevant authority),
3. the details of the request and the action taken is forwarded to Medicare and stored against the customer's history, and
4. The Clinical Intervention Team is notified and works with the individual on their problems.

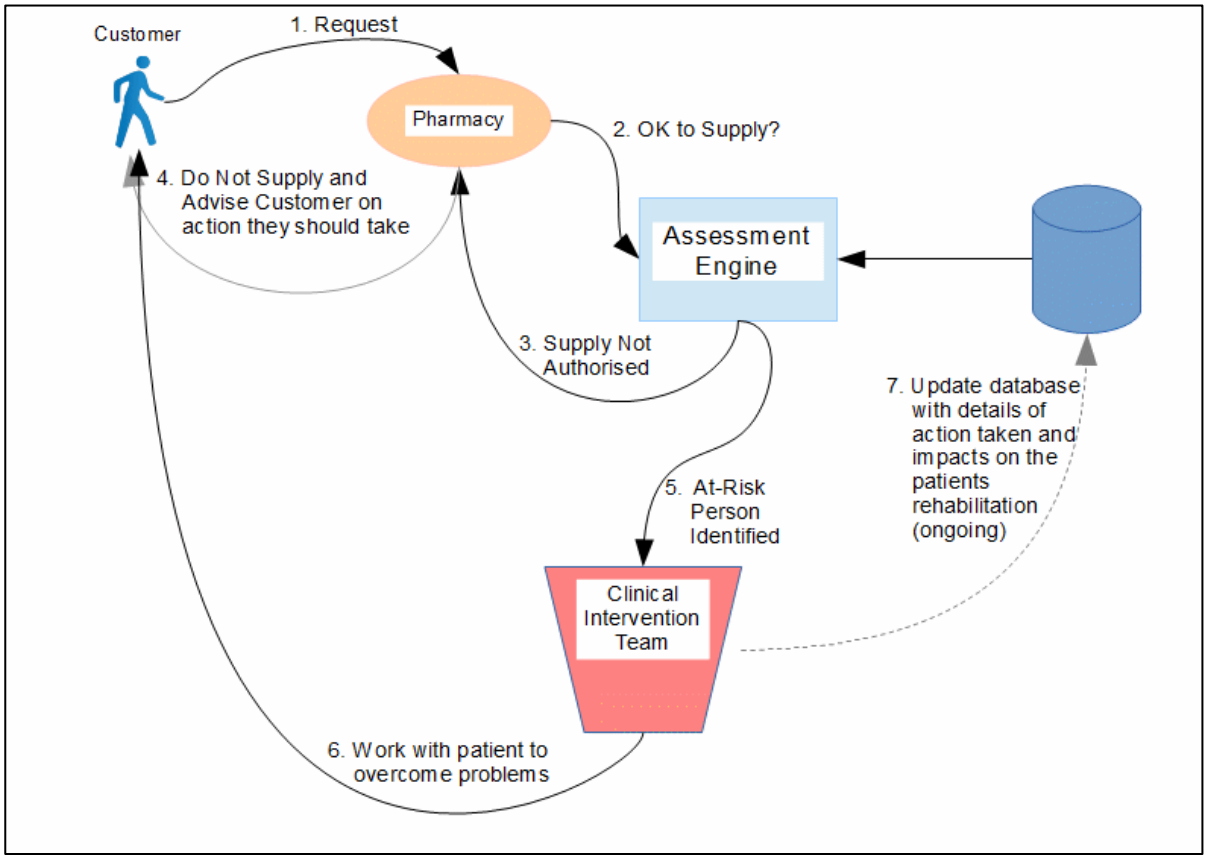

Figure 2. Alternate Process 1 – No Supply – At-Risk Person

Alternate Processes 2

Or, if at step 1 the individual's history shows the individual is nearing at-risk status:

1. the pharmacist can supply the medicine, and
2. the pharmacist is instructed to provide the customer with advice on the use of the drug and resources the customer should consider utilising, and
3. the details of the request and the advice provided is forwarded to Medicare and stored against the customer's history, and
4. follow up action with the customer may be taken by the relevant authority with all details stored against the customer's history.

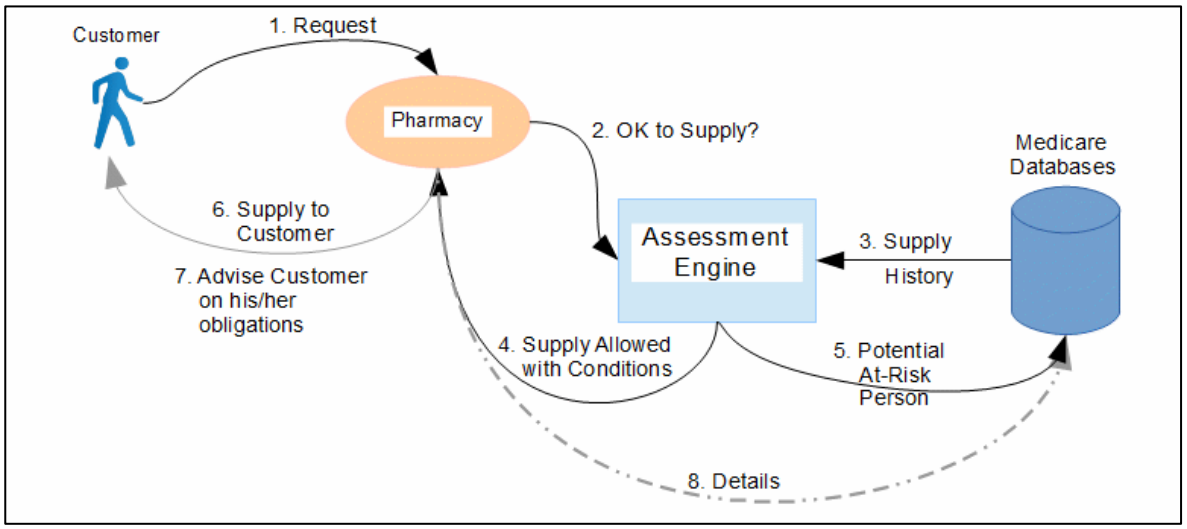

Figure 3. Alternate Process 2 – Potential At-Risk Person Identified – Supply with Conditions

Medical interventions should be based on clinical considerations, but as can be seen they can be initiated based on supply patterns and variations in the patterns. Indicators such as frequency of purchase and increased use could act as triggers and there could be an escalation process where for example education is tried first, then stronger methods can be employed.

Data Mining Potentials

Currently there is scant reliable information on the actual use of OTC codeine products as there is no way of collecting usage data other than in very small scale surveys.

It follows from this that there can be no reliable information on the numbers of users gaining quality of life benefits from these products. Nor can there be reliable information of any loss in quality of life benefits if these products are banned from OTC availability.

This proposal will assist in making these more visible and provide the means to facilitate both widespread and targeted deep delving epidemiological studies with full history of the patients purchases being available to researchers.

As well as providing data on the number of OTC users, it will have already occurred to the reader that this process will also identify those that do not use codeine products. Researchers are thereby provided with an identified pool of people to study for their pain management profiles who do not use codeine, something that they cannot easily do today.

I ask the committee to compare the type and quality of information on usage patterns it is using to make their decision today compared to the position they would be in after just 1 year of operation under this proposal.

Pre-Requisites & Necessary Conditions

One of the guiding principles should be to try to keep the potential addict within the system and to avoid losing them to drug dealers. Once they are in the domain of these dealers they are invisible to the medical system until it is too late.

To ensure maximum effectiveness in detecting and helping potential addicts, it is probably essential that the user feels comfortable with their relationship with the pharmacist and the medical establishment. To this end the process depends on their being no stigma or judgmental attitudes in obtaining OTC codeine products from pharmacies.

Australia's Unique Situation.

A unique set of circumstances exists in Australia:

- We have a population that is experienced in using codeine containing pharmaceuticals:
    - Codeine preparations have been available over the counter for more than 35 years;
    - A very large proportion of adult Australians will have met codeine prescribed at relatively high concentrations (e.g. [redacted]);
    - The low cost and ready availability of these pain killers over 3 decades means the population's use of codeine as pain relief should be in equilibrium and should have reached saturation.
- We have a universal health system which includes pharmaceuticals,
- Nearly every single Australian is known to the universal health system as a unique individual;
- The Information Technology supporting our health systems is sophisticated and is achieving high levels of information integration (a continuing trend);
- We have a universal health identifier for all Australians and could therefore identify a single patient through all interactions with health practitioners, specifically pharmacists and GPs;

- We have government organisations (DHS - Medicare and AIHW) that already track medical interactions and have sophisticated data mining capabilities;
- We have well developed medical research personnel and facilities.

In nearly every other country, either codeine is controlled or the country lacks a universal health systems to uniquely identify individuals or it has porous borders.

We have 35 years of widespread, general and unrestricted use of codeine enhanced analgesics and all long term health impacts should be known by now.

Considerations.

Some aspects of addiction are well studied, but as there is no mechanism for identifying at risk individuals at an early stage there is black hole in our understanding of how addiction progresses. Addicts only come to attention when they are fully addicted and well beyond early intervention. Any tool that would allow early identification of addiction would be an invaluable asset to the community's health.

I understand OTC sales are very high, indicating users in the order of millions. It is hard to understand why so many would go out of their way and spend so much money particularly as any purchase requires submission to an interrogation by pharmacy staff and a 'once over' by a pharmacist. There has to be good reasons for this demand but we lack any information on what these actually are and more importantly have no way of collecting this data.

Authorities do not have information on who purchases products OTC nor of changes to patterns of purchases. Pharmacies can supply the total number of items purchased but cannot relate this to the quantities sold to individuals. Changes in volumes or patterns of purchase, an early indicator of dependency in an individual cannot be captured with current systems.

Individual responses to codeine as a drug are quite variable, from nothing to highly addictive. While laboratory studies can target a few subjects, there is no tool to test codeine's effects across an entire population as there is no knowledge of who consumes it.

I suspect the most reliable submissions to the committee have been provided by clinicians dealing with patients with chronic pain or are suffering severe substance abuse effects. Patients in these groups have powerful and persuasive voices for the committee to hear. Those that use codeine infrequently do not have any voice. There is no organisation representing 'responsible' codeine users and the committee would be justified in believing such a group of users does not exist even if in reality there a million of them. It is understandable if the committee leans to considering only harm to the minority and is unaware of the benefits to the many of this medication.

From a quick reading of a very small sample of the literature it seems we know very little of how codeine preparations are used outside chronic pain suffers and addicts. What we do not know is

likely a fairly long list: how many people take these preparations, how frequently they take a dose, how many doses they take in an episode, the pattern of time between episodes, what things it is taken for, how often these things occur, how long they wait from onset of the pain until they take the medication, what options do they consider before taking codeine and what are the factors they consider, do they consider they need to maintain a personal supply margin or can they wait until they can obtain some and how does these preparations affect (negatively or positively) their ability to participate in normal activities.

Pain and addiction are depressing subjects and often disastrous aspects in our lives and it distresses me that medical science has not been able to make quicker progress on understanding these conditions. I would hope that, as true scientists, medical authorities would not pass up any opportunity to increase their knowledge of these areas. Just as I would hope they would choose to minimise harm without unduly restricting access by responsible adults to effective and useful medications.

Part 2: My Personal Perspective.

[redacted]

I am one of an unknown number of Australians that find 2 common analgesics totally ineffective while low doses of codeine to be extremely effective. Again as one of an unknown number I feel no 'buzz' from codeine and so am probably not at risk of becoming addicted. And after [redacted] years of exposure it is unlikely I would suddenly become addicted.

Contrary to dot point 3 of the reasons for the recommendation to the delegate – 'Purpose is questioned since benefit is low.' I can assure the committee that I do not consider the benefit of these products to be insignificant.

Looking back over a [redacted] year career there were times when OTC codeine products enabled me to overcome pain to the extent that I was able to get to work or able to continuing working and producing satisfactory results. I wonder what my employment pattern would have been without these medications – I would not have been so successful and quite possibly I would have found it hard to keep any reasonable well-paying job. In short my quality of life would have been far less than the one I led if I did not have access to OTC codeine.

I do not know why but I know that each of us feel pain differently and think it is self-centred as well as highly conceited for anyone to think everyone feels pain the same way they do. If anyone is fortunate enough to have a high threshold of pain they should not attempt to impose their

perceptions on others. And until science can measure pain objectively, those who suffer less should ask themselves if they, not the sufferers, are the odd ones out.

For the record I was a heavy smoker [redacted]. I have a personal understanding of addiction, having tried countless unsuccessful times to give up.

I therefore do not take codeine dependency lightly but I cannot accept the assumption that withdrawing codeine products from OTC will have no detrimental effects on my life. I suspect that I would ignore the warnings on paracetamol doses if codeine products are not available to me. I suspect I would take as many tablets as needed in the hope increased dosage would replicate the effects of codeine.

The immediacy of the pain and the need to mitigate it would far outweigh some possible long term consequences of paracetamol abuse.

It would be ironic if removing OTC codeine had the effect of increasing damage to the liver and other organs for millions of Australians who only take codeine in small infrequent doses. But it would be disastrous if it pushed those it is intended to help underground and into the arms of drug dealers especially as an alternative could keep them visible and within a support network.

I would like to thank the committee for the opportunity to comment and I hope I have not wasted you time.

The Secretary

Chemical Scheduling Secretariat

GPO Box 9848

CANBERRA ACT 2601

14TH October 2015

Re: Reasons for the scheduling delegate's interim decision and invitation for further comment for the ACMS, October 2015

To whom it may concern:

I would like to express my full support for the following interim decision in relation to the rescheduling of codeine.

Schedule 8 - Amendment

CODEINE except when included in Schedule ~~2, 3 or~~ 4.

Schedule 4 - Amendment

CODEINE when compounded with one or more other therapeutically active substances:

a. in divided preparations containing 30 mg or less of codeine per dosage unit; or a
b. in undivided preparations containing 1 per cent or less of codeine.

I also support the removal of the schedule 3 and schedule 2 entries.

I also express my support for the proposal implantation date of the 1 June 2016.

I thank the Committee and the Delegates for their consideration of this matter.

Kind regards

[redacted]

[redacted]

[redacted]

15 October 2015

Advisory Committee on Medicines Scheduling
Therapeutic Goods Administration
CANBERRA ACT

SUBMISSION ON INTERIM DECISION RECOMMENDING THAT OVER-THE COUNTER MEDICINES CONTAINING CODEINE BECOME PRESCRIPTION ONLY

I oppose the proposed restriction of codeine products to prescription only.

What will be achieved from such a change and if this change is made, what evidence does the TGA have that claimed drug dependence and adverse affects of these pain relieving medicines will decrease simply by changing the "method" by which people may access these medicines? Instead, what I anticipate from such a change is that there will be:

- a significant increase in Medicare costs to the taxpayer
- an increase in 'patients' and consequential increased income for medical practitioners
- other alternatives found by consumers which may have greater adverse impacts should access to basic pain relief be so restricted
- increased income for pharmaceutical companies working in partnership with doctors to peddle other drugs to this new and increased cohort of 'patients', including stronger pain reliving drugs (such as Oxycodone) leading to potential catastrophic consequences for people. There is significant evidence that thousands of Australians live as 'legal' drug addicts (with adverse side effects) and are kept dependent on their doctor(s) – courtesy of the *'prescription only'* pain relieving medicines. Given this reality, it beggars belief that the TGA would conclude that by shifting more people onto doctors, drug dependence (and adverse impacts) associated with pain relieving medicine will decline. This is an absurd argument and the evidence does not support such a conclusion

    - I have known many cases involving young people who have been given script after script by doctors for strong pain relieving medications over a long period of time – people 'doctor shop' and some doctors do not care (they are getting paid after all). It is utterly appalling that there are no consequences for what really amounts to legal drug pushing turning these kids into drug addicts. What is anyone going to do about that? Where is the accountability? Is it time for parents to file lawsuits? Based on current experience, doctors are unfit to be invited to be part of this solution – they need to get their own processes and prescribing practices under control first! It is borderline criminal and therefore, inappropriate for the TGA to give the green light to an expansion of such practices.

The TGA needs to understand and accept that Australia is a free society (or perhaps it is not) and as such, adults are capable of making their own decisions and choices about the substances they elect to put in their bodies. If people wish to use over-the-counter medicine then that is their choice - just as it is a person's choice to visit a doctor to obtain prescriptions for all manner of things. Personally, I do not agree with the latter as I subsidise such behaviours and I know that a lot of what is prescribed is harmful and unnecessary – but I

accept that this is their choice as adults to make an informed decision about what they are taking.

It galls me that by removing these medicines from pharmacies, the TGA is forcing additional costs onto me as a taxpayer. The argument for removing codeine based medicines from the 'counter' and forcing people to doctors is seriously flawed and gives rise to questions around undue influence being applied to the TGA by vested interests.

I have no confidence in the TGA given its narrow focused 'so-called solution' to reducing drug dependence on codeine products. The only winner by increasing the number of people attending doctors to obtain codeine prescriptions is the doctors themselves. It is obscene.

I would, however, have confidence in the TGA if it were to accept that there is a massive health workforce operating within Australia (other than doctors) who actually focus on wellness and care and healing of people which needs to be utilised to work with people to better manage codeine use and reliance. Instead, Australians are only being offered the option of increased reliance on doctors who are already the primary provider of drugs (through prescriptions) to people with a proven record of turning people into drug addicts.

In summary, the reality is that doctors peddle highly addictive drugs to Australians already through prescriptions – what makes the TGA think that by providing doctors with additional "so called addictive" drugs to select from will change that picture for people? All the TGA is doing is shifting the cost onto the taxpayer, making doctors wealthier and causing major inconvenience to consumers by restricting pain relief access – all of this for no net change in drug dependence. This is a very lazy way of attempting to solve a perceived problem.

My recommendation to the TGA is to get creative and innovative and support pharmacies to improve the current system and/or work with other health practitioners (other than doctors) – doctors are not the fountain of all knowledge – this I know to be true.

Thank you for the opportunity to comment on this matter.

[redacted]

Invitation for further comment on the interim decision to reschedule Codeine, following the August 2015 meeting of the Advisory Committee on Medicines Scheduling (ACMS #15)

To whom it may concern,

We appreciate the opportunity to provide further comment in support of the interim decision to recommend deletion of the current schedule 2 and 3 entries for codeine.

Our original submission, in support of the proposed change, focused on the public evidence of harm linked to codeine products, the limited efficacy of OTC codeine combination analgesics compared to other available analgesics, and the concerns held by Australian healthcare practitioners (pharmacists and GP's) about codeine use and abuse that were highlighted in a survey which [redacted] independently commissioned. We are pleased to see that the ACMS and the Scheduling Delegate have fully considered these particular issues amongst the relevant matters relating to scheduling, as outlined in section 52E of the Therapeutic Goods Act 1989.

We firmly believe that the objections raised against this proposed scheduling change, both in the submission process itself and subsequently within the media, do not adequately address these fundamental issues nor do they counter the weight of evidence that shows the relatively easy access to codeine products is having an increasingly harmful effect on the Australian public.

A key argument against the change seems to revolve around significantly increased costs to the public purse resulting from codeine patients having to visit their doctor as a consequence of any rescheduling. However, this disingenuous argument avoids the fact that there are alternative analgesics available ranging from plain paracetamol or ibuprofen, to alternative combination analgesics such as paracetamol-caffeine, or the newer paracetamol-ibuprofen combinations which are all available without prescription. Hence current codeine users do have suitable alternatives available without prescription and it can equally be argued that any patients not wanting to change from codeine could benefit from a full consultation with a medical practitioner given that codeine addiction is a well-documented effect.

In addition, the most recent issue of the Medical Journal of Australia includes a new study relating to the trends and characteristics of accidental and intentional codeine overdose deaths in Australia from 2000 to 2013, and we have attached a copy of this study for further reference. The results of this study further confirm the need for significant action in addressing the increasing incidence of harm and death relating to the use of codeine products in Australia.

We fully endorse the interim decision to reschedule codeine products, and see it as an essential step in further protecting the health of the general public from such products. Codeine products will still be available to the public with the recommendation of a doctor, but the intervention of

[redacted]

an appropriately qualified medical practitioner will establish whether there is a bona fide clinical need for its use, on an individual basis, and hopefully also assist in identifying individuals who need further assistance in dealing with possible codeine dependency.

Yours sincerely,

[redacted]

13 October 2015

Medicines.Scheduling@tga.gov.au

Further submissions on TGA's interim decision on a proposal to up schedule codeine

[redacted] does not support the proposal to reschedule codeine combination products from Pharmacist Only (S3) to Prescription Only Medicine (S4).

[redacted] supports the need to have safe, appropriate access and availability, we believe that the current S3 Pharmacist Only scheduling provides this.

Over the counter codeine combination products have been proven to be substantially safe and effective analgesics. Pharmacist-consumer dialogue enables pharmacists to intervene if they believe that the medicine is not appropriate to the consumer's ailment of symptom. They are also able to communicate directly to the consumer on aspects of safety of the medicine.

Furthermore, we are not convinced that rescheduling the medicines will offer a greater disincentive to those consumers intent on misusing or abusing them, than that currently provided by Pharmacist Only status.

Yours faithfully,

[redacted]

[redacted]

Submission to TGA

Re-scheduling Codeine Products

I strongly object to the proposed deletion of the Schedule 3 entry for codeine products, and the rescheduling of all codeine containing compound products to Schedule 4.

As a resident of a remote regional community in Western Australia, suffering pain symptoms from degenerative disease due to injury, I have limited access to routine Doctor Care due to the well documented difficulties in attracting and retaining Medical Practitioners in regional Western Australia.

Additionally, I have no access to realistic ancillary health care providers such as physiotherapy, massage, chiropractor etc. The closest services available to me are 235km away from my home town. Self-medication is an important part of my personal health care regime, including access to Nurofen Plus, as required, from our local Pharmacist. This TGA decision to ban 'over the counter' sales of products like Nurofen Plus was clearly made without regard to remote regional residents.

Our local chemist is the only Pharmacy in our region, an area greater than the size of the state Victoria. Nearest alternative services are 235km south from my hometown and over a 1000km in other directions.

For the TGA to seek to limit my access to the resources I need to manage my health, in order to offer some degree of benefit to a very, very small group of vulnerable people - who live in much heavier populated regions, with greater access to health care providers - is incomprehensible to me, and here is why:

> I bear regular witness to State and Federal Government bodies withdrawing all manner of essential health and social services from our region as 'cost cutting' measures. Essential Services removed from our region in the last 12 months include:
>
> - the only Midwife in the region;
> - Aboriginal Women's Health Services working closely on Foetal Alcohol Spectrum Disorder and chronic Domestic Violence issues;
> - Drug and Alcohol Counsellors;
> - Breaking the Cycle Project Officer;
> - Child Protection Officers;
> - Best Beginnings/Early Childhood Workers etc

Abuse of Alcohol and Other Drugs, including 'Ice', is having a profound impact on the lives of the majority of people living in this region, and is escalating in magnitude as more and more health and diversionary/management services are withdrawn, or cancelled.

To now witness that same Government monster dedicating significant financial and manpower resources to an agenda that will specifically supresses my personal options of health care self-management beggars belief – and I do object, in the strongest terms!

It is difficult to comprehend the mindset behind the recommendation to curtail the role of the community Pharmacist in this matter. Our Pharmacist literally knows everyone who regularly seeks his products – isn't he the best weapon on the ground if the TGA is genuinely concerned about over the counter codeine abuse?

By taking this proposed action, the TGA will be deliberately targeting ordinary citizens who require pain management to maintain their quality of life. Despite 'expert opinion' claiming little benefit to consumers using these 'over the counter' products, it is my personal 'expert opinion on my body' that they are of great benefit to me, when I do need them.

To summarise, the greater number of ordinary citizens, such as me, who are in a situation where there may not be a Doctor, will be significantly adversely affected by this poorly researched and ill thought out decision.

There is a danger in the wider community that the proposed Rescheduling of Codeine products will place a significant additional burden on health care/Medicare costs, by directing more people towards Doctor access (if they have one to access!).

Where does the TGA propose to direct consumers in my circumstance - to the local Publican (we do have 4 Hotels in the region) or the local Illicit Drug Dealer??

[redacted]

[redacted]

[redacted]

15th October 2015

Response to the Delegate's interim decision to reschedule Schedule 2 and 3 codeine products to Schedule 4.

[redacted] 15 October 2015

A meeting of the Advisory Committee on Medicines Scheduling recommended to the TGA medicines scheduling delegate that codeine be removed from Schedules 2 and 3, but be retained in Schedules 4 and 8, because of concerns about misuse, addiction and harm from misuse. On 1 October 2015 the medicines scheduling delegate announced an interim decision to accept this recommendation.

Codeine.
Codeine (methylmorphine) is effectively an inactive prodrug of morphine requiring bioactivation to morphine by the enzyme CYP2D6. The degree of bioactivation is unpredictable and depends on the phenotype of the individual. Few people know their phenotype, which can only be determined with an expensive test that is seldom used prior to codeine use.

- Some cannot metabolise codeine to morphine and receive no analgesic benefit.
- Others are ultra-rapid metabolisers and are at risk of morphine toxicity, and may be at increased risk of addiction. This is a patient safety concern. Morphine toxicity in adults has been reported. Overdose deaths of children treated with codeine have been reported, and of breast-fed infants of ultra-rapid codeine metabolising mothers.

Because of these deaths several countries have reviewed controls over codeine.

- The US FDA has taken action relating to ultra-rapid metabolising mothers breast-feeding, and treatment of children post-operatively, because in these circumstances a number of deaths have been reported.
- The European Medicines Agency is also reviewing codeine safety and taking regulatory action to control harm resulting from the unpredictability of codeine metabolism.

In October 2015 the Australian Therapeutic Goods Administration recommended that[1]:

- codeine is contraindicated in children younger than 12 years
- codeine is contraindicated for children from 12-18 years after adenotonsillectomy for obstructive sleep apnoea
- warnings contraindicating use of codeine for breast-feeding mothers should be consistent
- education of professionals, patients and caregivers regarding the variability of codeine efficacy, and the possibility and recognition of morphine overdose due ultra-rapid metabolism of codeine

Regardless of the medicines scheduling delegate's final decision, it is important that the last of the TGA's recommendations above is implemented.

[1] Therapeutic Goods Administration. Codeine use in children and ultra-rapid metabolisers. Pharmacovigilance and Special Access Branch Safety Review. Version 1.0. Therapeutic Goods Administration, Department of Health, Canberra, October 2015.

OPPOSITION TO THIS INTERIM DECISION INCLUDES A NUMBER OF THEMES.

Theme: There will be considerable costs to Medicare and the consumer if codeine is removed from over-the-counter availability.

The Australian Self Medication Industry (ASMI) represents companies involved in the manufacture and distribution of non-prescription consumer healthcare products in Australia. It funded a study by Macquarie University examining the value of over-the-counter (OTC) medicines in Australia[2].

It is not known whether this research was published in a peer-reviewed professional journal where it would be available for critical scrutiny.

One of the questions consumers were asked is what they would do if they could not get Pharmacist only analgesics over the counter. The study described that a large proportion responded that they would go to a doctor. It used these results to calculate the cost to the system of this change. Estimates included almost $170 million cost to Medicare for additional doctors' visits, and, $70 million paid by individual consumers.

Since 1 October 2015 these figures and estimates of cost have been widely quoted by those opposed to the delegate's interim decision to reschedule codeine medicines to Schedule 4.

The study was conducted in December 2013, and circumstances have changed since then, so these results and estimates are no longer relevant to the current situation. Since the study in December 2013 two brands of Schedule 3 combination analgesics combining paracetamol with ibuprofen have become available, are heavily promoted, and increasing their share of the S3 analgesic market. In [redacted] share of adult analgesics increased from 8% in 2011 to 29% in 2013, competing with combination products such as the analgesics category leader [redacted], which held 30% value share in 2013[3].

- [redacted] (ibuprofen 150 mg/paracetamol 500 mg) was included in the Australian Register of Therapeutic Goods (ARTG) on 23 December 2013, and
- [redacted] (ibuprofen 200 mg/paracetamol 500 mg) included in the ARTG on 4 July 2014.

These combination products provide superior analgesia to the current OTC codeine analgesics available from a pharmacist. Recent Cochrane systematic reviews compare the relative effect size of different OTC analgesics, describing the number needed to treat (NNT) after a painful operation for one patient to achieve a 50% or more reduction in pain. Results were as follows:

- Ibuprofen 400 mg/paracetamol 1000 mg — NNT 1.5
- Ibuprofen 400 mg/codeine phosphate 25.6-60 mg — NNT 2.2
- Paracetamol 1000 mg/codeine phosphate 60 mg — NNT 2.2

Fewer than 2 patients receiving ibuprofen/paracetamol need to be treated for one to achieve this analgesic benefit, whereas more than two require to be treated with either of the codeine combination analgesics, even including studies at the higher codeine doses.

One randomised trial demonstrated that 1 and 2 tablets of the single-tablet combination of ibuprofen/paracetamol were statistically significantly more efficacious than 2 tablets of paracetamol/codeine. One tablet was found to provide a similar level of analgesia to the

[2] Macquarie University. The value of OTC medicines in Australia. Macquarie University, March 2014.
[3] Euromonitor International. Analgesics in New Zealand. July 2014. http://www.euromonitor.com/analgesics-in-new-zealand/report Accessed 11 October 2015.

ibuprofen/codeine combination, and 2 tablets provided significantly superior pain relief to ibuprofen/codeine[4].

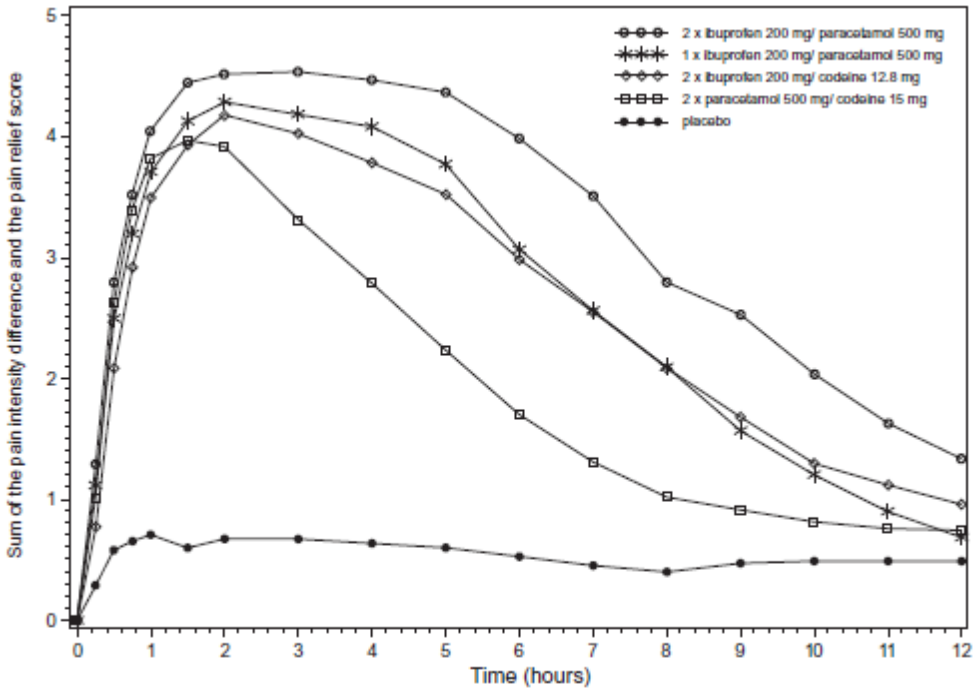

Fig. 2. Mean pain relief and intensity differences shown at each time point (intention-to-treat population).

Under these changed circumstances, when consumers are unable to obtain OTC codeine analgesics from a pharmacy if they are rescheduled, they will still be able to successfully self-medicate acute pain, with a bonus of not being exposed to the risk of codeine addiction, and without the need to go to a doctor for a prescription for codeine analgesics.

Theme: Removal of OTC access to cough suppressants and "cold and flu' preparations will disadvantage consumers.

Cough is one of several defensive mechanisms protecting the airway and clearing mucus and foreign material from the airway and lungs[5]. On occasion it becomes unproductive and troublesome.

Consumers may seek help from a pharmacist for cough associated with upper respiratory infection. There are multiple causes of cough, any many causes other than acute infection, such as chronic obstructive pulmonary disease or chronic bronchitis will usually be better treated by a medical practitioner who may target the underlying cause, and manage cough in the context of overall management of this condition. Treatment of cough with high doses of codeine is associated with side effects[6].

[4] 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;152:632–642.

[5] Banner AS. Cough: Physiology, evaluation, and treatment. Lung 1986;164:79-82

[6] Chung KF. Currently available cough suppressants for chronic cough. Lung 2008;186:82-7.

Acute viral upper respiratory tract infection (the common cold) affects most humans at some time, and cough is its most frequent symptom[7]. Billions of dollars are spent worldwide seeking relief from this multi-symptom condition. Thousands of non-prescription, over-the-counter products are available worldwide, aimed at relieving various common cold symptoms.

Cough is to some degree responsive to voluntary suppression[8]. Placebo effect plays an important part in the response to cough suppressants[9]. A review of placebo effect in cough suppression notes that all over-the-counter cough medicines (OTC) are very effective treatments because of their placebo effect. The placebo effect is enhanced by expectancy related to advertising, brand, packaging, and formulation, as well as pharmacist recommendation.

There is little evidence that codeine provides a clinically useful antitussive effect.
A study investigated the effects of codeine syrup B.P. (30 mg/10 ml, q.d.s.) or syrup vehicle on cough frequency and the subjective severity of cough[10]. Cough frequency and subjective scores of cough severity were significantly decreased but at no time point was there a significant difference between the codeine- and placebo-treated groups. The results indicate that codeine, either as a single 30-mg dose or in a total daily dose of 120 mg, is no more effective than the syrup vehicle in controlling cough associated with acute upper respiratory tract infection.

A systematic review of randomised controlled trials of over-the-counter cough suppressants, including those incorporating codeine, concluded that they cannot be recommended because there is no good evidence of their effectiveness[11].

Theme: Pharmacy monitoring of Schedule 2 and 3 codeine supply is an alternative to rescheduling.
Nielsen sales figures show about 1.3 million packets of over the counter products such as Nurofen Plus and Panadeine Forte are sold in Australia each month in a sector worth about $145 million a year[12]. This amounts to about 15.4 million packs per year, each requiring sale by a pharmacist after establishing a therapeutic need, making an assessment of whether the patient was codeine-seeking, and providing advice about use.

Assuming that there are 5,300 pharmacies in Australia and that they work on average 6 days a week provides an estimate that collectively there were 1,653,600 million days Australian pharmacies were open for business. To estimate the average number of packs supplied per day in Australian pharmacies, dividing 15.4 million by 1,653,600 million yields an average number of packs supplied each day to be 9.3 packs.

Monitoring would require additional time to establish identity, document details about the customer and the supply, and manage those customers who may be identified as obtaining multiple packs or obtaining packs more frequently than clinically necessary.

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[7] Eccles R et al. Treatment of Acute Cough Due to the Common Cold: Multi-component, Multi-symptom Therapy is Preferable to Single-Component, Single-Symptom Therapy—A Pro/Con Debate. Lung. Published online September 2015

[8] Widdicombe J, Eccles R, Fontana G. Supramedullary influences on cough. Respir Physiol Neurobiol. 2006 Jul 28;152(3):320-8.

[9] Eccles R. Importance of placebo effect in cough clinical trials. Lung. 2010;188:S53-61.

[10] Eccles R, Morris S, Jawad MS. Lack of effect of codeine in the treatment of cough associated with acute upper respiratory tract infection. J Clin Pharm Ther 1992;17:175-80.

[11] Schroeder K, Fahey T. Systematic review of randomised controlled trials of over the counter cough medicines for acute cough in adults. BMJ 2002;324:1-6.

[12] Brown R. Doctors and pharmacists call for tighter controls on codeine due to rise in addiction. Sydney Morning Herald. September 14, 2014.

Assuming an average additional time of 5 minutes to operate monitoring, this would add an extra 46.5 minutes a day to a pharmacist's time demands.

Pharmacists are busy, and as competition increases with increasing franchising of pharmacies, and rising costs caused by price disclosure/PBS cuts, discounts, open ownership pressure and rising rents creating cost pressures, pharmacists have responded that these cost pressures would force them to start cutting costs and counteract their loss in income. A 2014 study prior to the Sixth pharmacy agreement reported that pharmacies were looking to reduce cost by reducing staff wages or hours to replace an expected loss of revenue[13].

In a submission to the National Drug Misuse Strategy, the Pharmacy Guild of Australia commented on the effects on pharmacy of greater controls[14]. It noted that restrictions could have a negative effect on pharmacy workflow, reducing the capability of pharmacists to meet all of their professional obligations, citing as an example the 1 May 2010 rescheduling of OTC codeine combination analgesics from Schedule 2 to Schedule 3. It described that this had a significant impact on pharmacy workflow, and that patients would have to wait until the pharmacist was available to assess each request. There would also be a significant impact on the pharmacist's capacity to effectively perform their professional obligations, particularly pharmacies with only one pharmacist on duty. Greater demands on their time may risk that some aspects of their work would be neglected, and this would affect the public from a safety and/or quality of care perspective.

Added monitoring of OTC analgesics not integrated into workflow would burden pharmacists with substantial additional time-demands that may have an adverse effect on pharmacy workflow and may distract from their professional practice.

Theme: Delaying implementation until introduction of monitoring.
Pharmacists and their organisation, and industry, have known about the serious problems arising from the supply of OTC codeine analgesics since it was first raised at the National Drugs and Poisons Schedule Committee in 2007. Numerous media articles, cases and case series published in medical and pharmacy professional journals, the rescheduling on 1 May 2010, and advanced notice of a submission to the Advisory Committee on Medicines Scheduling in early 2015 recommending rescheduling to Schedule 4 of OTC codeine analgesics, has provided ample warning that a change might be forthcoming. Industry will have to adjust production schedules to account for the proposed rescheduling in seven months from the announcement of the final decision.

Delaying introduction would continue to place numerous vulnerable Australians at risk of misuse, addiction, and serious adverse effects.

Theme: The vast majority of Australians use OTC codeine analgesics as recommended.
No evidence is cited for this assertion, but even if it is true, the more important thing is whether there is a proper balance between risk and benefit, and whether the level of harm is acceptable.

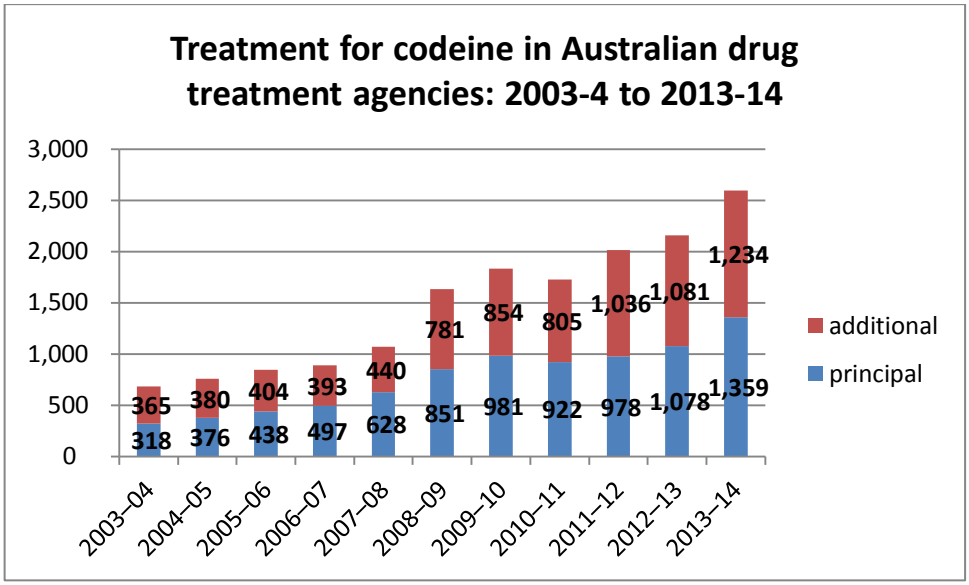
With more than 250 published Australian and New Zealand cases of serious harm from misuse of OTC codeine/ibuprofen analgesics described in my previous submission (Attachment 1), and evidence that hundreds of people have sought pharmacotherapy for opioid dependence on codeine, or treatment at alcohol and drug centres, and that the latter is increasing, the level of harm is unacceptable.

[13] University of Technology Sydney. UTS Pharmacy Barometer 2014.
[14] Pharmacy Guild of Australia. Comments by the Pharmacy Guild of Australia on the discussion paper to support the development of the National Drug Misuse Strategy (NPDMS).

Additional documentation of serious harm involving OTC codeine analgesics is provided in a paper published in the Medical Journal of Australia several days after the announcement of the delegate's interim decision. The paper examined trends in codeine-related mortality in Australia, noting a greater than doubling of overall rate of codeine related deaths, from 3.5 per million ln 2000 to 8.7 per million in 2009[15]. Among those cases where there was information about whether the source of codeine was a prescription or an over-the-counter drug (572 cases). Prescription opioids were recorded in 343 (59.9%), and OTC codeine products in the remaining 229 (40.1%).

The number of individuals treated for codeine dependence in Australian public drug treatment agencies has increased every year since 2003-04 except for 2010-11 when OTC codeine was rescheduled to Schedule 3[16]. In 2013-14 there were 2593 treatment episodes for codeine - 1359 where it was the principal drug of concern, and 1234 where it was an additional drug of concern.

These figures do not include treatment occurring in private clinics, general practice, or treatment by addiction medicine physicians. Since those affected by addiction to OTC codeine analgesics differ from those requiring treatment for stronger prescription opioids[17], being more likely to be female, employed, and using only one drug. Prescription drug misusers generally differ from illicit drug users, with less severe opioid use, less intravenous drug use, and greater social stability [18]. Accordingly they may be less likely to seek treatment in publicly funded alcohol and drug agencies, and not be counted in these figures.



It is evident that combining codeine with simple non-opioid analgesics provides little analgesic benefit, and the risk to benefit ratio is unsatisfactory. There is an unacceptable level of harm.

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[15] Roxburgh A et al. Trends and characteristics of accidental and intentional codeine overdose deaths in Australia. Med J Aust 2015;203:229.e1-229.e7.

[16] Australian Institute of Health and Welfare 2015. Alcohol and other drug treatment services in Australia 2013-14. Drug Treatment Series no. 25. Cat. no. HSE 158. Canberra: AIHW.
Table SD.9: Closed episodes provided for own drug use, by principal drug of concern and all drugs of concern, 2003–04 to 2013–14

[17] Nielsen S et al. Comparing treatment-seeking codeine users and strong opioid users: Findings from a novel case series. Drug Alc Review 2015;34:304-11.

[18] Sigmon SC. Characterizing the emerging population of prescription opioid abusers. Am J Addict 2006;15:208-12.

[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] 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 Codral products have been responsibly and safely used by millions of Australians since at least 1977 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 Codral 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 Codral 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. JJP 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 Codral 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 Codral 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 Codral, 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 Codral 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.

JJP 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 Codral 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 Codral products were efficacious (the benefit) then repeat purchase would never occur, irrespective of what marketing or retail campaigns are put in place. Codral 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.

Codral 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 Codral 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] already 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 Codral. 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 Codral 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 JJP.

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.

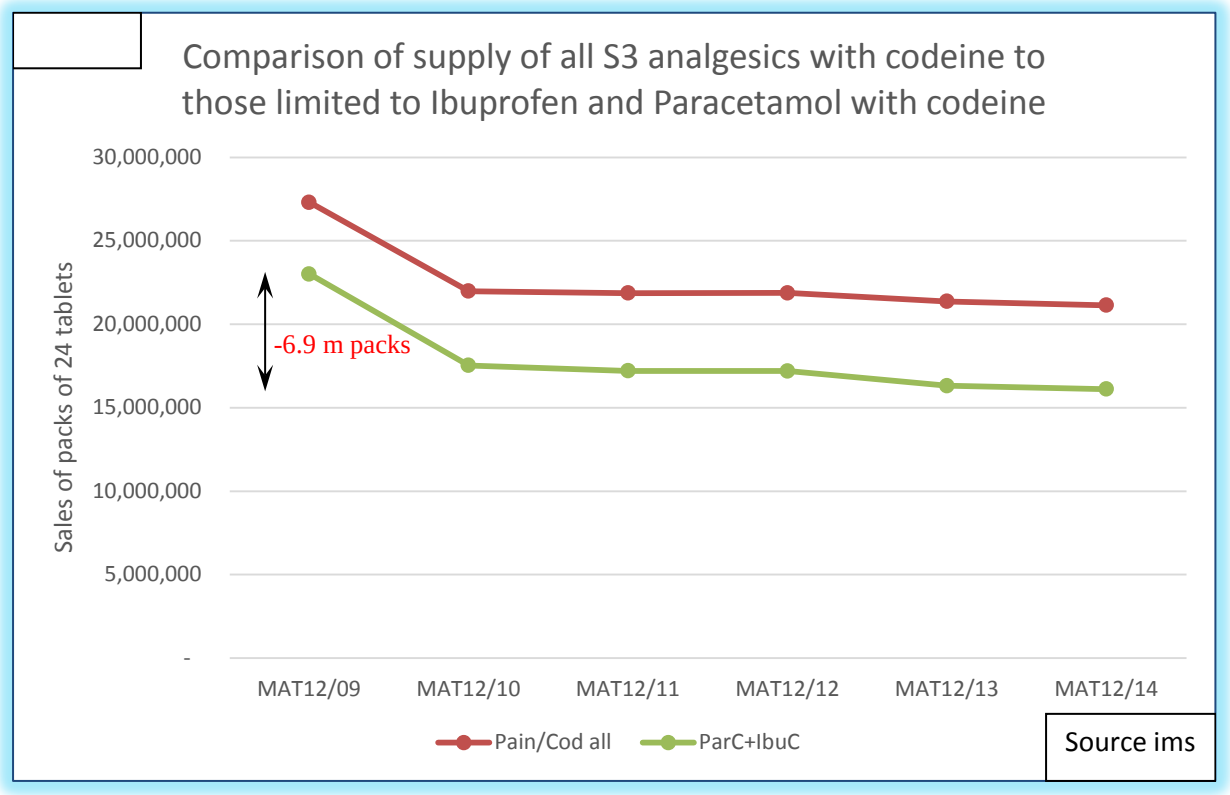
Roxburgh also concludes that *"Codeine-related deaths (with and without other drug toxicity) are increasing as the consumption of codeine-based products increases"*. IMS data clearly demonstrates that since the up scheduling of codeine containing analgesics in 2010, there has been a significant decrease 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, Codral 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 Panadeine ® 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 Codral 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 Codral (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 Codral has been available for a very long period of time (since at least 1977) 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 Codral 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**.

Codral 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. JJP 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.

[redacted] 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.

[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.
[9] Matts SG. A clinical comparison of Panadeine Co., soluble codeine co., soluble aspirin in the relief of pain. *Br J Clin Pract* 1966 October;20(10):515-517.
[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, Gorta 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 JJP, 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:**

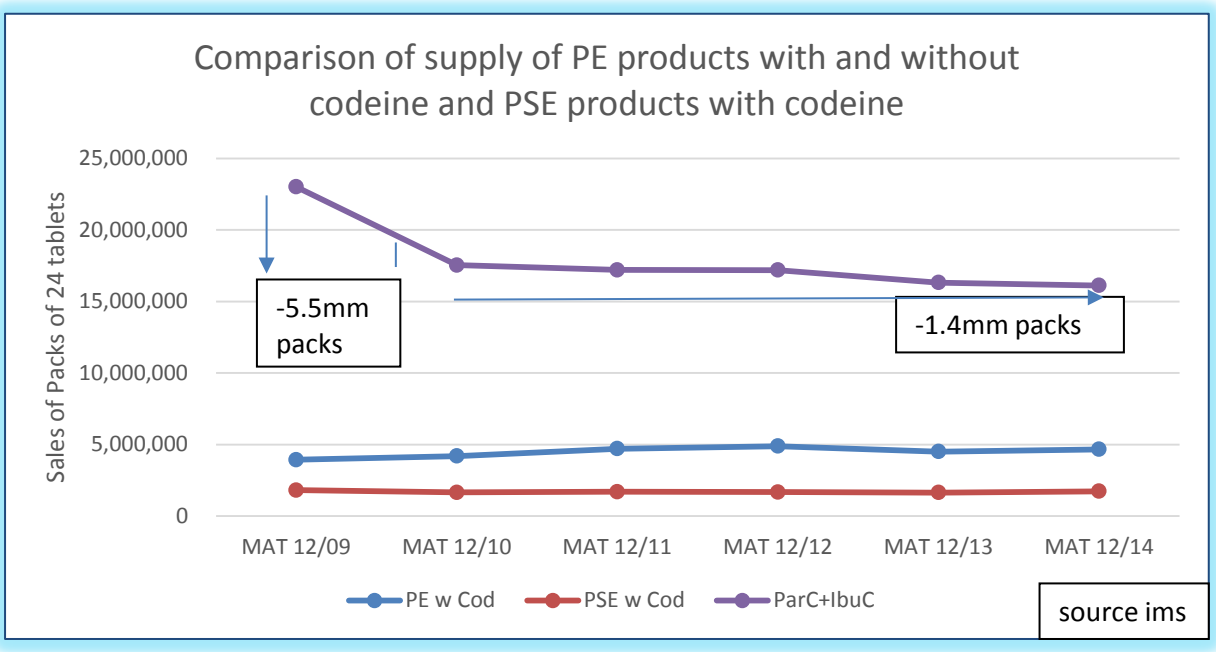
There is no robust evidence to substantiate this comment. This is not relevant for codeine containing cold and flu preparations.

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 [redacted] and with the Chief Pharmacist of the NSW State Department of Health [redacted] Data specific to New Zealand was shared with Medsafe [redacted] 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.

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 Codral 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."

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]