Comments on Agenda Items for the 55th meeting of the Medicines Classification Committee on Tuesday 3rd May 2016

Public Consultation

Medsafe
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29 March 2016

Hannah Hoang
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Ministry of Health
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Comments on proposed agenda items for the 55th meeting of the Medicines Classification Committee

Dear Hannah,

Thank you for the opportunity to provide comment on the following proposed agenda items for the 55th meeting of the Medicines Classification Committee (MCC):

> 5.1.1 Oral contraceptives – objection to the proposed reclassification from prescription medicine to restricted medicine
>
> 5.2.1 Updating the guidance document titled 'How to change the legal classification of a medicine in New Zealand' to include the publication of additional information submitted in objections

Background

Family Planning is a key stakeholder in sexual and reproductive health care, including the reclassification of oral contraceptives. We are New Zealand's largest provider of sexual and reproductive health services and information. We operate 30 clinics throughout New Zealand, as well as school and community-based services and serve over 140,000 patients annually. Our health promotion teams run professional training and workshop programmes in schools and the community for young people, parents, teachers and other professionals. We are a registered private training establishment offering clinical training and development for doctors, nurses and other clinicians – including pharmacists.

In March 2014, Family Planning provided comment on the initial proposal for the reclassification of selected oral contraceptives and made the following recommendations:[1]

1. Allow more primary care nurses to prescribe contraception by reviewing the protocols for nurse prescribing through the Nursing Council.
2. Assess the proposed move to pharmacist supply of oral contraception for its potential effects on health equity and reducing disparities.
3. Ensure high-quality training of non-medical providers of oral contraception, especially in the assessment of risks to women's health, teaching how to take pills correctly, and training in sensitive treatment of women seeking contraception.
4. If the proposed change occurs, we recommend:
    - the use of Collaborative Practice Agreements (where a pharmacist works with a doctor who audits their practice)
    - the training programme is at least 2 days duration, and
    - pharmacists should first supply continuing combined pills only, and progress to the supply of initial combined pills once assessed as competent.

We provide comment below on the alternative proposal from Green Cross Healthcare which was accepted at the 54th meeting of the MCC. We were not aware of the alternative proposal until the meeting minutes of the 54th meeting were published.

Our comments reiterate the recommendations of our previous submission and provide additional remarks for your consideration. We also provide feedback on the Medicines Classification Committee (MCC) consultation processes referenced in agenda item 5.2.1.

Agenda item 5.1.1

- As the alternative proposal for reclassifying oral contraceptives was not available for broad consultation prior to the 54th meeting, we support the position of the College of General Practitioners which calls for a full and appropriate consultation with all relevant stakeholders on the alternative proposal before finalising a decision to reclassify oral contraceptives. We encourage the MCC to consider the proposal in the context of the impact on health equity and reducing health disparities.

- We strongly support increased access to the full range of contraceptive options for all women and access to comprehensive sexual and reproductive health care. It is unclear how this proposal will contribute to this outcome. There is no indication which pharmacies will offer oral contraceptives without a prescription to women who have previously been prescribed an oral contraceptive within the last 3 years, in which regions and communities, and how the services will be integrated with other sexual and reproductive health care. There is a possibility that this

[1] Family Planning submission to MCC dated 26 March 2014.

service may only be accessible to motivated women who can afford to pay for unsubsidised oral contraceptives and the cost of the pharmacist consultation. As such, it does not address the equity issues which contribute to poor sexual and reproductive health in many marginalised communities. Women in these communities should benefit from changes in classification of contraceptive methods.

- We maintain our position that nurse prescribing should be advanced as a way to increase access to contraception and to reduce fragmentation of care. Nurses, including Family Planning and community based nurses, are already well-trained and well-placed to prescribe oral contraceptives. Nurses are skilled in clinical assessment and already work in communities of high need.[2]

- It is our understanding that women who have had a prescription for oral contraceptive pills, but have run out of pills, are already able to access a short term emergency supply from a pharmacist without obtaining another prescription.[3] While this would only be useful for women who have recently run out of pills, it is relevant to consider that this facility already exists for pharmacists.

- We agree with the College of General Practitioners that three years is a long time between health assessments. A woman assessed three years ago for an oral contraceptive prescription may present to a pharmacist with significantly different health needs and risks. This may incur a cost for the assessment without provision of pills and the cost for a further visit to Family planning or a GP. As we recommended for the initial proposal, pharmacists providing this service should be required to be adequately trained in assessing risk and providing guidance on effective pill taking.

- Family Planning reiterates its concern about the small but real risk of serious – and potentially fatal – complications from the use of combined oral contraceptives (COC). As we stated in our previous submission, Family Planning's experience is that it is common for even well-trained health professionals to find it difficult to ascertain if migraines, for example, are the type that contraindicate a COC. It is important to assess a range of risk factors in assessing suitability for COC because individual factors can combine to pose an unacceptable risk. For example, simple migraine and smoking are two risk factors which on their own do not contraindicate COC, but together they are contraindications for COC.

- Family Planning reiterates support for comprehensive training of pharmacists offering this service, including the use of collaborative practice agreements where the pharmacist works

[2] Nursing Council of New Zealand, 2014. Application for consideration of designated prescribing rights. Retrieved from: http://www.nzdoctor.co.nz/media/3546094/application_for_registered_nurse_prescribing_primary_health_and_specialty_teams.pdf.

[3] Medicines Regulations 1984 (SR 1984/143), 44 (m). Retrieved from: http://www.legislation.govt.nz/regulation/public/1984/0143/latest/whole.html

closely with a doctor with expertise in contraceptive provision. We believe an initial audit by a doctor is an essential part of any training programme. It is also important that pharmacists maintain competence. A regular review of appropriate practice should be built into any training programme.

Agenda item 5.2.1

- Family Planning finds the MCC's consultation process unclear. We support a comprehensive review of the process rather than the minor update to the guidelines being proposed. It does not appear that the MCC proactively seeks feedback on proposals from key stakeholders and the public. Most organisations do not have the resources to continually check the Medsafe website for updates and additional information. MCC does not appear to have a process for distributing information to a list of interested parties or broadly publicising consultations as Pharmac does.

- The fact that this is the third time that MCC will consider the issue of the reclassification of oral contraceptives raises considerable questions about the effectiveness of the decision making and consultation processes.

- Family Planning believes that MCC should place greater emphasis on proactively engaging all stakeholders, including academics and researchers, organisations and the public, on any proposals for reclassification of medicines.

Thank you for the opportunity to provide comment.

Ngā mihi

Jackie Edmond
Chief Executive

GREEN CROSS HEALTH

11th April 2016

The Secretariat
Medicines Classification Committee
Medsafe
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Dear Committee members,

Re: **Submission for the 55th meeting of the Medicines Classification Committee**

We are pleased to provide the Medicines Classification Committee with the following submission for the 55th meeting of the Medicines Classification Committee in response to agenda items.

Item 5.1.1 Oral contraceptives

We continue to believe that selected oral contraceptives should be available to NZ women 16 years and over without a prescription. Ideally this should allow pharmacists to initiate therapy as well as continue supply, however, we have suggested in previous submissions a scenario in which a doctor has prescribed the oral contraceptive first.

We note that the evidence we have provided for previous meetings has been extensive showing that trained pharmacists can supply these, and that women themselves can ascertain their suitability for treatment (see previous applications). The evidence we have provided shows safety that is in line with non-prescription availability, and the MCC has agreed that the risk-benefit profile of the medicine is in line with non-prescription availability. We have selected only the safest oral contraceptives, and outlined a model in which pharmacists would be trained for the supply and screening tools and patient information is used. This model is followed in many Western countries now for pharmacist-administered vaccines, and has worked extremely well in NZ with the emergency contraceptive pill since 2001. We have provided evidence to the committee before of the workability of the model through qualitative research and quantitative research with trimethoprim.

We note the increasingly widening access to oral contraceptives in the Western world.

The Association of the Bar of the City of New York, specifically the Committee on Science and Law, and the Committee on Sex and Law have written to the Governor of New York State and

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the Food and Drug Administration (FDA) in February 2016 to urge New York State and the country to make oral contraceptives more readily accessible. The letters are available at:

http://www2.nycbar.org/pdf/report/uploads/20072992-OvertheCounterContraceptionScienceLawSexLawletter232016state.pdf

http://www2.nycbar.org/pdf/report/uploads/20072992-OvertheCounterContraceptionScienceLawSexLawletter232016federal.pdf

The US Center for Reproductive Rights has put out a 20-page document on over-the-counter contraception, as at February 2016. It is called Over The Counter: the Next Big Step for Birth Control. We have attached this document which is also available at http://www.reproductiverights.org/sites/crr.civicactions.net/files/documents/USPA_OCOTC_Report_Final_Web_2.16.compressed.pdf

We provide some recent evidence on oral contraceptives that is of interest.

In a paper published this year, Grindlay and Grossman[1] surveyed US women who were aged 18-44 years, sexually active and not pregnant or seeking pregnancy. One-third of women who tried to get prescription contraception reported difficulties doing so. The most common difficulties were cost barriers (14%), challenges obtaining an appointment or getting to an appointment (13%), a medical visit with a pap smear/pelvic exam being necessary before getting a refill (13%), and not having a regular doctor or clinic (10%). Difficulties getting a prescription were more likely to be experienced by women who were uninsured, who were Spanish speaking, and who were unmarried in a de facto relationship.

A qualitative research project[2] in 138 women through 14 focus groups targeting African American, Asian American, and young American women found interest in women being able to access oral contraceptives without prescription. Current barriers to access included difficulty knowing where to seek care, scheduling an appointment, taking time off work, arranging transportation and wait times. Teenagers not wanting to tell their parents about the use was a barrier, including to getting to a clinic. Benefits perceived of availability through pharmacies included removal of barriers including wait time, transport, cost, and taking time off work. A further benefit was reducing the potential for gaps in therapy when women were on holiday or forgot to get a prescription before running out. Some participants thought a pharmacy would provide increased privacy and comfort over a clinic, and anonymity for teenagers who did not want their parents to know, with the following quote provided:

> *I think it would be more comfortable for younger people because it would save them from being nervous, because if you go to a clinic everybody knows you're at a clinic. And you only go to a clinic for that kind of stuff like birth control or STDs and stuff like that. (South Carolina, age 13–22)*

Some of the teenage participants thought it would make teenagers more likely to access the oral contraceptive owing to convenience and privacy, others thought adverse event concerns or cost would still be barriers for teenagers.

Concerns participants had was about the knowledge of pharmacists, and potential lack of comfort or privacy at the pharmacy. Some participants, concerned about the safety among first-time users and young women, considered a health care provider needed to be visited

before initiating oral contraceptives. However, all women of all ages (including 13 year olds) were confident they personally could take an over-the-counter oral contraceptive. Some participants thought it might encourage early sexual experiences, others disagreed. The authors noted an alternative to the "true OTC availability" that appeared to be presented to the women was the model used in some states of a specially trained pharmacist screening women and providing advice.

A survey was sent via participating national professional organisations for doctors and midlevel providers to their members providing reproductive health services.[3] The response rate was low (19%), and 60% were doctors, and 36% were midlevel providers (e.g. nurse practitioner, physician assistant, nurse-midwife). Three-quarters supported pharmacist-initiated oral, transdermal and vaginal contraceptives. Fewer supported a behind-the-counter model (45%) or general sales availability (28%). Two-thirds supported pharmacist-initiated injectable progestogen contraceptives. Doctors were slightly more supportive in both cases than midlevel providers, but this was not significant. Multiple reasons for the support were chosen, including important to expand access and reduce barriers (92% of doctors), preventing unintended pregnancies is an important health issue (91%), greater accessibility for adolescents (83%), and important to foster a multidisciplinary approach to public health (58%). Most participants thought screening could decrease.

At the last meeting the following recommendation was made, before being returned to the next meeting for consideration:

That the selected oral contraceptives (desogestrel, ethinylestradiol, norethisterone and levonorgestrel) should be reclassified as restricted medicines, when sold in the manufacturer's original pack containing not more than six months' supply by a registered pharmacist who has successfully completed a training programme (endorsed or accredited by an organisation that is to be confirmed as stated in the following recommendation), when indicated for oral contraception in women who have previously been prescribed an oral contraceptive within the last 3 years from the date of an original medical practitioner's prescription.

That Green Cross Healthcare Limited should provide Medsafe with details of who will be responsible for accrediting the training programme and maintaining and enforcing the provisions under which a pharmacist with additional competencies could prescribe selected oral contraceptives.

In response to this request in the case of the reclassification of oral contraceptives Green Cross Health will work together with the Pharmaceutical Society of New Zealand and the Pharmacy Council of New Zealand to have the appropriate training in place for pharmacists.

That Green Cross Healthcare Limited should update Medsafe of the changes required to the training and monitoring procedures to reflect the Committee's recommendations. We confirm that this will be incorporated into the training.

That market sales should be collected and analysed to monitor the success of the scheme in improving access to oral contraceptive pills. The Committee is interested in being updated on the outcomes of this recommendation. We confirm this will occur.

We were also pleased to see the comments made by the New Zealand Medical Association in print in NZ Doctor on 27th January 2016 in response to the above mentioned recommendation of the MCC that stated, "**NZMA chair Stephen Child says the association is pleased about the convenience the decision offers and it will not be lodging an objection before the 9 February deadlines"** The full article can be viewed at the following link: http://www.nzdoctor.co.nz/news/2016/january-2016/27/pill-reclassification-for-pharmacy-'a-fair-call'-says-nzma.aspx

Item 6.3 Albendazole

We do not support this reclassification. We have a number of concerns about the application for albendazole to become available as a pharmacy-only medicine, including inconsistency in the application about indications (pharmacists would not be treating hydatids), and the expectations around the handling of pregnancy. Albendazole may not be available anywhere else in the Western world without prescription for human use. It is not licensed for use currently in NZ or in the UK (according to the British National Formulary).

The primary use for anthelmintics in New Zealanders is for *Enterobius vermicularis* 'threadworm', a very common problem in children (and their families). The currently available treatments, mebendazole and pyrantel work well for this condition; any new therapy would have to have at least the same safety and efficacy. The BNF states mebendazole is the "drug of choice" for threadworms. For medicines likely to be used in children and women of child-bearing age or who may be breast-feeding (their mothers), the benefit-risk of any reclassified medicine needs to reach a high standard, and we have outstanding concerns.

Item 6.4 Loratadine

We do not support the reclassification to a 10-day pack

In NZ and in most of the Western world, pack sizes for general sales availability of systemic treatments are limited, usually to a few days' supply (Table 1). This limitation of pack sizes maximises safety, limiting how many can be taken should someone take the whole pack in one day, or if two different brands containing the same medicine were inadvertently taken (consumers largely being unaware of generic names of non-prescription medicines), and leads to a reflection on the need for further treatment or advice from a doctor or pharmacist at the end of the supply.

Table 1 General sales pack sizes of medicines for systemic use

Medicine	Restrictions
Paracetamol	Maximum 10 g (i.e. 20 x 500 mg tablets, or 2.5 days' supply at 5 g/day)
Ibuprofen	Maximum 25 x 200 mg tablets (just over 4 days' supply)
Phenylephrine	Maximum 250 mg per pack
Dextromethorphan	Maximum 600 mg per pack
Ranitidine	Maximum 7 days' supply
Aspirin	Unrestricted (while probably a historical anomaly, review would be wise)

Our concerns are:

1. People behave differently with medicines in supermarkets – data from Australia and the US suggests they do not respect them as medicines. Medicines in supermarkets have limited pack sizes for good reason, because there is a need to think about whether or not you need to continue a medicine, and to reduce the risk of taking too much or not treating an underlying condition.

2. Risk of taking excessive doses.

3. Risk of inadequate or inappropriate treatment of the condition, with consequent effects on work and school performance

4. Use in children under 12 years despite the labelling

5. The precedent being set for greater packs to be in the supermarket without healthcare professional input

6. The focus on health literacy to ensure a person understands the risks and benefits is not met with a larger pack size being made available in supermarkets.

These concerns are outlined below.

There is no additional benefit to increasing the pack size available in supermarket.

There is no real benefit in terms of convenience for patients from increasing the pack size in the supermarket. Pharmacies are far more prevalent than supermarkets, and conveniently located,

so are more likely to be easier for most people to access than the supermarket, and almost all pharmacies are open six or seven days each week, and often open until 6pm or later.

People with allergic conditions can take a short course of antihistamine available from the supermarket. For people with long-term allergies, it would be more appropriate to see a healthcare professional where a review could ensure they have the most appropriate treatment long-term and have discussion about allergen avoidance, particularly where they have co-existing eczema or asthma, or where their illness is not responding well to antihistamines.

The concerns in greater detail:

1. People behave differently with medicines in supermarkets.

Many people think medicines available outside of pharmacies are safe.[4,5] Surveys from the US where non-prescription medicines are available from any outlet are telling. Nearly half (41%) of US consumers believed OTC medicines will not cause problems because they are weak.[5] A third of US consumers took more than the recommended dose of an OTC medicine to make it more effective, and 36% combine medicines when they have multiple symptoms, risking overdosing.[5] Most Americans didn't know what ingredient was in their OTC analgesic.[5] In America, oral OTC analgesics are "used frequently, often inappropriately, and there is an alarming rate of ignorance regarding the potential side effects of NSAID and OTC analgesics".[4] Two US telephone surveys reported together found 26% of adults using OTC analgesics and no prescription analgesics used more than the recommended dose (1997 survey) and 44% (2002 survey).[4] In comparison, 8% of adults using prescription analgesics and not OTC analgesics took more than the recommended dose (1997 survey).

In the Netherlands, most OTC medicines are sold from drugstores or supermarkets. Drugstores do not have a pharmacist in the store. A study there found 13% of consumers recruited from medical practices and deemed high risk (with contraindications and precautions to NSAID use) reported using an OTC NSAID in the past month, mostly purchased from non-pharmacy outlets (79%), and mostly high dose aspirin or ibuprofen,[6] despite pack warnings. Pharmacy supply in those who were high risk was associated with increased information provided (compared with drug stores or supermarkets), and it was unknown how many consumers were prevented from purchasing the product through pharmacy advice. Taking OTC NSAIDs for more than 7 days was common, both in those who were high risk (33% of those taking OTC NSAIDs) and those who were not high risk (23%). Most Dutch consumers lack confidence in the general population to choose and use OTC medicines safely.[7] Indeed, a Dutch task force aiming to reduce hospitalisations from adverse reactions to drugs recommended moving aspirin and other oral NSAIDs to pharmacy-only to reduce risk, because it was considered safer.[8]

In Australia, the move of ibuprofen from pharmacy-only to general sales was associated with significantly increased use in people with contraindications, precautions or interactions according to telephone surveys.[9]

The usage of vaginal antifungals rose 85% in the US on the move from prescription-only to general sales,[10] while in Sweden (where a prescription to pharmacy-only change occurred) an overall smaller increase was seen.[11] Such a difference is likely to reflect increased inappropriate

use where healthcare professional oversight did not occur, as indicated by a US study on non-prescription vaginal antifungal use.[12]

There is no peer-reviewed published research about usage of general sales medicines in NZ and very little information from health systems similar to NZ. We can only extrapolate from elsewhere. The US shows problems with this category of medicines as noted above, Australia shows greater inappropriate use when ibuprofen went from pharmacy-only to general sales. In NZ we do not know how often children are treated inappropriately with medicines from the supermarket, we do not know how often recommended doses are exceeded. We do not know if multiple drugs with the same ingredient (prescribed or available from the supermarket) are

being combined. Without quality academic NZ research to inform reclassifications from pharmacy-only to general sales, a cautious approach is needed.

2. Risk of taking excessive doses, including by people with hepatic impairment

Antihistamines take time to reach peak effect, typically a few hours after reaching the maximum plasma concentration.[13] This provides ample opportunity to redose multiple times to try to get a benefit. Antihistamines also are effective in mild to moderate allergic rhinitis, but as the pollen count increases their effect wanes, increasing the chance of a person exceeding the recommended dose if they have not discussed their allergic rhinitis with a health professional. Expecting a medicine to be safe owing to its availability in the supermarket, and not having had any advice at the supermarket on use of the medicine will increase the likelihood of such behaviour.

Consequences of excessive doses may be particularly important in people with hepatic impairment, on interacting medicines (including erythromycin, quinidine, fluoxetine, fluvoxamine, and probably ritonavir), or in children, elderly, or pregnant or breast-feeding women. There is no ability to access any advice around contraindications, precautions or interactions in a supermarket. Information on drug interactions has largely been limited to regular dosing of loratadine; it is unknown what effect a higher dose would have.

With overdose, anticholinergic effects and sedation can be expected according to the datasheet and literature.[14] Such sedation can cause drowsiness and impair driving or other tasks for which concentration is important. It is often stated that non-sedating antihistamines should be more correctly termed as having minimal sedative effects when given at recommended doses, as CNS impairment does occur at excessive doses for terfenadine, loratadine, mizolastine, and cetirizine.[15]

A review of the non-sedating antihistamines stated that: *"all the mentioned second generation antihistamines are clearly less sedating and impairing than their predecessors, but none of them is entirely devoid of CNS activity".*[14] A further review stated: *"More recently, however, it has become evident that all antihistamines have the potential to produce subjective and/or objective sedation, depending on their concentration, histaminergic mechanisms involved in the control of CNS arousal and the sensitivity of tests used to detect changes in CNS activity."* [16]

Obviously there is a need to see evidence that there is no sedation if taken at greater doses than those recommended, given the potential behaviour with a medicine in the supermarket.

An association has been found with antihistamines (including non-sedating antihistamines) and weight gain, central obesity and increased insulin concentration.[17] Weight gain has been found in some placebo-controlled studies including with non-sedating antihistamines.[18,19] While loratadine does not include this in its New Zealand datasheet, it is possible that weight was not measured in the long-term clinical studies. Antipsychotics with potent H1 blocking properties (e.g. olanzapine) have considerable weight gain. Cyproheptadine (an older antihistamine) is used to aid weight gain in underweight individuals. Increased use of antihistamines and inadvertently or intended increased dosing from availability in the supermarkets could potentially increase the burgeoning problem of weight gain in the NZ population.

Given the points made above, that consumers have low awareness of active ingredients in OTC medicines,[5] and that consumers expect supermarket medicines to be safe, inadvertent double or even triple dosing is likely. The fact that a few years ago advertising to the public stopped requiring active ingredients to be stated in the ad would not help. No one in the supermarket would query a purchase of two or more different packs containing loratadine – unlike in a pharmacy. Furthermore, using the supermarket medicine in addition to the prescribed loratadine is likely This behaviour would be particularly concerning in someone with hepatic impairment, or a child, might cause increased sedation, and is not in line with quality use of medicines.

3. Risk of inadequate treatment of the condition, with consequent effects on work and school performance

It is common in community pharmacy to have people in December and January entering the pharmacy wanting to buy an antihistamine and when asked if the medicine is working well for them admitting with considerable frustration that it really isn't but they are purchasing it without knowing the options. Antihistamines help mild to moderate allergic rhinitis, but as the season progresses and the pollen count increases they often become inadequate. They also work poorly on nasal congestion, which can affect sleep. Pharmacists can recommend a corticosteroid nasal spray with the antihistamine or refer them to their doctor if it is possibly not an allergy causing the symptoms. They can also talk to them about related conditions, e.g. asthma, which may also need to be addressed, and avoidance of allergies.

There is no ability to access any advice around condition or treatments in a supermarket.

4. Use in children under 12 years despite the labelling

A medicine in a supermarket is likely to be considered to be safe in children in the perception of parents and caregivers. Treatment in young children requires consideration of the condition (cold or allergy) and concurrent illnesses (is there wheeze or night-time cough, signs of infection?) Dosing in a young child with a pack from the supermarket may be incorrect. Under treatment of the allergic rhinitis and other allergic conditions (e.g. asthma) in young children may occur through not having medical review or involvement from the pharmacist. Early diagnosis of childhood allergic rhinitis is important to ongoing management.[20]

There is no ability to access any advice around condition or treatments in a supermarket, nor around interactions (e.g. erythromycin may be used in a child's respiratory infection and an antihistamine may be taken in addition)

5. The precedent being set for greater packs to be in the supermarket without healthcare professional input

Pharmacy only medicine is more suitable for larger packs of medicines.

6. The focus on health literacy to ensure a person understands the risks and benefits is not met with a larger pack size being made available in supermarkets.

We have already highlighted in the other points above of how research shows some people do not comply with labelling on products available in a general sales environment, and show limited understanding of the appropriate usage of the product.

To summarise, there are potential risks with the reclassification and little benefit to the consumer. There is no need for a 10-day pack to be available as General Sales.

Item 8.2.1b: Hydrocortisone with antifungal to pharmacy-only medicine

We do not support the suggested reclassification of an antifungal with hydrocortisone to go to pharmacy-only medicine. We believe that a pharmacist should always be actively involved in the supply of these medicines. As a pharmacist-only medicine currently, they are not available for self-selection in the pharmacy, and the involvement of the pharmacist and recording of the details sends a clear message with these medicines to take care with them. The pharmacist needs to find out why the hydrocortisone is needed and in particular will be watching for use in nappy rash, and particularly ongoing use to "prevent nappy rash" noting the effect of the nappy in occluding the area, as well as secondary bacterial infections that can occur in tinea pedis. Furthermore, hydrocortisone should only be used when inflammation or itch is not troublesome, and therefore restricting its availability to the pharmacist would ensure this is the case, and that the patient knows to move to antifungal alone for when the problem has eased. With a recommendation to use the azole antifungals for up to 4 weeks to solve tinea pedis, and a recommendation not to use hydrocortisone for such a length of time, there is potential for confusion. The pharmacist guides patients well through this, indicating to change to azole alone for the required time, or better still, providing a faster acting treatment such as terbinafine to maximise compliance and have the problem resolved quickly.

The NZ Formulary states about miconazole plus hydrocortisone:

> *"extreme caution is required in dermatoses of infancy including nappy rash—treatment should be limited to 5–7 days"*

And on compound topicals including corticosteroids it states:

"The advantages of including other substances (such as antibacterials or antifungals) with corticosteroids in topical preparations are uncertain, but such combinations may have a place where inflammatory skin conditions are associated with bacterial or fungal infection, such as localised infected eczema. In these cases the antimicrobial drug should be chosen according to the sensitivity of the infecting organism and used regularly for a short period (typically twice daily for 1 week). Longer use increases the likelihood of resistance and of sensitisation."

There is little potential benefit to consumers of the suggested reclassification and we believe that a pharmacist should be involved in the supply and self-selection is not appropriate.

Item 8.2.1.d Naloxone to pharmacist only medicine

We are supportive of the reclassification of Naloxone to Pharmacist Only medicine when used for the treatment of opioid overdose.

Please do not hesitate to contact me should you require further information or clarification.

Yours Sincerely,

ALISON VAN WYK
Executive – Professional Services
Green Cross Health

References:

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[redacted]

4 April 2016

The Secretariat
Medicines Classification Committee
Medsafe
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Dear Sir/Madam,

Re: The 55th meeting of the Medicines Classification Committee

My comments on three agenda items are below. Please note that any agenda items I have not commented on simply reflects my current workload and is not to imply support or otherwise of the item.

5.1.1 Oral contraceptives

I support the oral contraceptive reclassification, preferably including initiation of supply and where women have had the oral contraceptive previously. I am disappointed that New Zealand women have had to wait another 6 months (or two thirds of a baby) for access that is reasonable, evidence-based and has been well-considered.

8.2.1 b. Hydrocortisone with antifungals

As a pharmacist who has worked in many community pharmacies I have considerable concern about the proposal to reclassify this combination to pharmacy-only. The pharmacist plays an important role in aiding reasonable self-medication with this medicine. Inappropriate long-term use of this medicine and use on skin conditions that do not warrant a topical steroid, or for which a topical steroid is inappropriate is more likely to occur without the pharmacist's active involvement in the supply, and where the consumer can self-select the product. Because hydrocortisone may reduce inflammation it could seem to be effective in circumstances in which its use is inappropriate. Long-term use on babies would seem likely without the clear safety message to the consumer of the pharmacist-only category. I would not want to see this medicine be supplied without active involvement of a pharmacist. This reclassification has little benefit for the consumer, who can still obtain the medicine from the pharmacist, but increases the risk of harm.

8.2.1 d. Naloxone

While not being able to comment on the need within New Zealand for this service, or the likely uptake, I note that support in Australia was considerable from multiple organisations including addiction organisations, individual opioid users, and individual health care professionals involved in their care. Other Western countries also have increased access to naloxone. This reclassification is reasonable from a public health perspective. I would expect appropriate information to be created for pharmacists to ensure appropriate and safe supply, either by or with involvement from pharmacists' professional organisation and/or appropriate organisations in the field of addiction, and suggest that any change is delayed until this can occur.

Yours sincerely,

[redacted]

[redacted]

Dame Margaret June Sparrow DNZM MBE
BSc MBChB DipVen FAChSHM HonDSc FRANZCOG(Hon)

2 April 2016

The Secretary
Medicines Classification Committee
Ministry of Health
committees@moh.govt.nz

Dear Secretary

Re: Agenda 55th Meeting Medicines Classification Committee
5.1.1 Oral Contraception – objection by RNZCGP

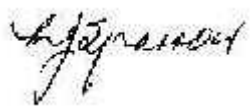
As an experienced sexual health physician I wrote previously (29 September 2015) to support the application of Green Cross Health and the Pharmacy Guild of New Zealand for the reclassification of selected oral contraceptives from prescription medicine to restricted medicine when supplied for oral contraception by a registered pharmacist who has successfully completed a training course in accordance with an approved protocol.

I write again to support this option which represents my preferred position for the reasons previously stated to improve access.

The alternative option that supply is permitted by specially trained pharmacists only to women who have been previously prescribed oral contraceptives (supported by RANZCOG) I regard as a compromise. I am disappointed that even this moderate proposal has resulted in an objection on the grounds of process.

The prevention of unintended pregnancies is too important to be lost sight of in organisational and collegial disputes.
I attach separately the MCC Public Consultation Cover Sheet.

Yours sincerely



Dame Margaret Sparrow DNZM MBE

New Zealand Medical Association
Te Hauora mō ngā Iwi Katoa

4 April 2016

Hannah Hoang
Advisor Science (Secretariat for MAAC & MCC)
Committee & Support Services
Product Regulation
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By email: committees@moh.govt.nz

Agenda for the 55th meeting of the Medicines Classification Committee

Dear Hannah

The New Zealand Medical Association (NZMA) wishes to provide comment to the Medicines Classification Committee (MCC) regarding the agenda for the 55th meeting scheduled for 3 May 2016. Our feedback is limited to item 5.1.1 on the objection to the proposed reclassification of selected oral contraceptives from prescription medicine to restricted medicine.

1. The NZMA is New Zealand's largest medical organisation, with more than 5,500 members from all areas of medicine. The NZMA aims to provide leadership of the medical profession, and to promote professional unity and values, and the health of all New Zealanders. Our submission has been informed by feedback from our Advisory Councils and Board.

2. We support the objection raised by the Royal New Zealand College of General Practitioners (RNZCGP) regarding the Committee's recommendation of reclassifying selected oral contraceptives from prescription medicine to restricted medicine. We draw your attention to our letter of 12 February 2016 (attached) in which we formally register our concerns with the process followed by the MCC as well as our support for the RNZCGP's proposed remedy to address these concerns.

3. We note that the alternative proposal to reclassify selected oral contraceptives from prescription medicine to restricted medicine would enable pharmacists to supply selected oral contraceptives to women *who have previously been prescribed an oral contraceptive*. In addition to the procedural concerns which we have outlined in our letter of 12 February 2016, we seek clarification as to whether, under the alternative proposal, a pharmacist could supply *any* oral contraceptive to a woman or only those oral contraceptives which have been previously

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prescribed. We are disappointed that references to support claims in the alternative proposal have not been identified or made publicly available.

4. We have evaluated the alternative proposal against our position statement 'Principles of Workforce Redesign'[1] and concluded that our previous concerns remain valid. We remain opposed to the alternative proposal for the following main reasons:

- We are not convinced that the requirement for a prescription constitutes a significant barrier to accessing oral contraceptives in New Zealand. Furthermore, we believe that any existing concerns about access to the oral contraceptive pill can be satisfactorily and safely addressed via a delegated collaborative model of prescribing, available under the Medicines Amendment Act 2013.

- One of the most important aspects of prescribing the oral contraceptive pill is the advice and counselling about its use and about sexual health in general, particularly for younger females. It is difficult to envisage how this can be done well in a pharmacy setting. It can sometimes be difficult even for experienced clinicians to broach sexual health when dealing with a young patient. In some cases, the patient will present asking for advice on contraception or sexually transmitted infections (STIs), but in the majority of cases, opportunistic intervention will be necessary. In our experience, teenagers are seen at general practice less than once a year, on average. As such, the potential for opportunistic medical interactions, as well as the act of forming a therapeutic relationship with a medical practitioner at a time of personal change, is already low. It is our view that the proposed reclassification would undermine the opportunity for opportunistic intervention and screening for at risk behaviours in an important patient group.

- The use of oral contraceptives is associated with risks that must be carefully considered before they are used and during their use. For example, combined oral contraceptives increase the risk of stroke in women who suffer from migraines with aura. They should not be started by women of any age who suffer from migraine with aura.[2] Combined oral contraceptives also increase the risks of venous thromboembolism (VTE) and are contraindicated for women with a current or past history of VTE and best avoided for those at high risk.[3] Various drugs interact with oral contraceptives to potentially decrease their efficacy, and it is important that patients are fully aware of these. Before prescribing oral contraceptives, therefore, it is necessary to obtain a thorough medical history, including cardiovascular risk factors, concurrent medications, allergies, and health problems (past and current). In many instances, a physical examination may be indicated (eg, when there is a suspected STI). We are not convinced that pharmacists will necessarily capture the requisite information to ensure the safe use of these medicines.

- Medsafe's most recent Prescriber Update featured an article on the increasing incidence of Idiopathic Intracranial Hypertension (IIH), and drew attention to the association between this potentially fatal condition and contraceptives.[4] Doctors are urged to be aware of this link—especially in women who are obese and taking contraceptives or other medications associated with the condition. We ask the Committee to consider whether

[1] Available from http://www.nzma.org.nz/__data/assets/pdf_file/0018/1458/Principles-of-Health-Workforce-Redesign-2013.pdf
[2] Roberts H. Combined oral contraceptive: issues for current users. BPJ April 2012(12):21–9. Available from www.bpac.org.nz/BPJ/2008/April/docs/bpj12_contraceptive_pages_21-29.pdf
[3] Ibid
[4] Medsafe. Prescriber Update Vol. 37 No. 1, March 2016. Available from http://www.medsafe.govt.nz/profs/PUArticles/PDF/Prescriber%20Update%20March%202016.pdf

pharmacists will be able to recognise the significance of the signs and symptoms arising from IIH (eg, headache, diplopia and pulsatile tinnitus).

- We believe that the proposed reclassification of selected oral contraceptives from prescription to restricted medicines is likely to further fragment patient care, with potentially serious consequences for patients, including unintended pregnancy or life-threatening adverse events. While we welcome the requirement to "inform [the patient's] GP of supply" we note that this is contingent on obtaining patient permission. It is possible, therefore, that many General Practitioners may not ever know (or only come to know too late) that their patient has re-started oral contraceptives. Current limitations in the shared electronic health record may also mean that pharmacists may not have access to key relevant patient information to safely prescribe oral contraceptives.

5. Modification of the proposal to cover pharmacist supply only to women who have previously been prescribed an oral contraceptive is inadequate to allay the concerns we have flagged. The proposal does not describe the minimum standard of care for pharmacist prescribing of the oral contraceptive. Furthermore, it does not designate lines of responsibility and accountability if something goes wrong. We also draw the Committee's attention to the fact that the majority of prescriptions for oral contraception are written by General Practitioners, not Obstetricians and Gynaecologists. We understand that the RNZCGP is opposed to the amended proposal.

6. We note that the guidance document on how to change the legal classification of a medicine in New Zealand is focused primarily on a risk-benefit analysis of a proposed reclassification.[5] We believe that the guidelines for the MCC must be broadened so that the Committee can take into account contextual factors such as impacts on fragmentation of care and opportunistic screening in its decision making. A focus solely on the direct effects of a medicine when considering reclassification reflects an erroneous assumption that prescribing is a discrete activity. Prescribing is inextricably linked with diagnosis, evaluation of general health and wellbeing, and represents an opportunistic point for screening/intervention. In addition, the information arising from this interaction should contribute towards improving the quality of information in an integrated health record.

7. We urge the MCC to stand by its original recommendation with respect to oral contraceptives (ie, these should remain prescription medicines), and to widen its decision criteria to ensure that it is able to take into account contextual factors when making recommendations on reclassification of medicines.

We hope that our feedback has been helpful and look forward to learning the outcome of this consultation.

Yours sincerely

Dr Stephen Child
NZMA Chair

[5] Medsafe. How to change the legal classification of a medicine in New Zealand. Guidance Document. June 2014. Available from http://www.medsafe.govt.nz/downloads/How_to_change_medicine_classification.pdf

NZMA
New Zealand Medical Association

12 February 2016

Hannah Hoang
Advisor Science
Medsafe
Ministry of Health
133 Molesworth Street
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By email: Hannah_Hoang@moh.govt.nz

Response to the minutes of the 54th meeting of the MCC

Dear Hannah

The New Zealand Medical Association (NZMA) understands that the Royal New Zealand College of General Practitioners (the College) has raised the following concerns with the minutes of the 54th meeting of the Medicines Classification Committee (MCC) Held on 24 November 2015 and released on 27 January 2016.

- the minutes are not accurate
- the process followed by the MCC in reaching a decision on the classification of the OCP is administratively unsafe – and may result in a decision that creates a risk of harm to patients.

The NZMA wishes to register its support of these concerns. We are also in support of the College's proposed remedy to address these concerns, namely, that the MCC should:

- append an explanation to the minutes of the 54th meeting to make clear that the MCC was mistaken in its assumption that the alternative proposal submitted by Green Cross Healthcare Ltd had been made publicly available
- Conduct a full and appropriate consultation with all relevant stakeholders on the alternative proposal before finalising its decision to reclassify the OCP
- Conduct a thorough review of its consultation processes to ensure that in future these are transparent, proactive, open, robust, and include safeguards to protect against regulatory capture.

Yours sincerely

Dr Stephen Child
NZMA Chair

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PHARMACEUTICAL SOCIETY
of New Zealand Incorporated

4 April 2016

Medicines Classification Committee Secretary
Medsafe, Wellington
via email: committees@moh.govt.nz

Dear Sir/Madam

MEDICINES CLASSIFICATION COMMITTEE (MCC)
COMMENTS TO THE 55TH MEETING AGENDA 3 May 2016

Thank you for the opportunity to submit comments on the Agenda for the 55th meeting of the Medicines Classification Committee.

The Pharmaceutical Society of New Zealand Inc. (the Society) is the professional association representing over 3,000 pharmacists, from all sectors of pharmacy practice. We provide to pharmacists professional support and representation, training for continuing professional development, and assistance to enable them to deliver to all New Zealanders the best pharmaceutical practice and professional services in relation to medicines. The Society focuses on the important role pharmacists have in medicines management and in the safe and quality use of medicines

Regarding the agenda items for the above meeting of the Medicines Classification Committee, The Pharmaceutical Society would like to note the following comments for consideration:

5 MATTERS ARISING
5.1.1 Objection to recommendation made at the 54th Meeting: Oral contraceptives – proposed reclassification from prescription medicine to restricted medicine

The Pharmaceutical Society would like to note we were unaware of the details of the "alternative" proposal for the repeat supply of the oral contraceptive, as considered by the committee at the 54th meeting. After reviewing the minutes of the 54th meeting, we are seeking clarification of the decision to approve repeat supply by pharmacists.

We have previously communicated with the Chair of MCC regarding the note for Green Cross Healthcare Ltd to provide Medsafe with details of who will be responsible for accrediting the training programme and maintaining and enforcing the provisions under which a pharmacist with additional competencies could prescribe selected oral contraceptives. As the responsible authority for the pharmacy profession, the Pharmacy Council is responsible for ensuring pharmacists' competence to practice. The Society, as the professional body representing all pharmacists in all areas of practice, considers itself has having the principal responsibility for developing and setting professional practice standards and guidance for pharmacists.

We also seek clarification of the intended model for "repeat supply".
The minutes of the 54th meeting state the recommended classification to be:

> *That the selected oral contraceptives (desogestrel, ethinylestradiol, norethisterone and levonorgestrel) should be reclassified as restricted medicines, when sold in the*

manufacturer's original pack containing not more than six months' supply by a registered pharmacist who has successfully completed a training programme (endorsed or accredited by an organisation that is to be confirmed as stated in the following recommendation), when indicated for oral contraception in women who have previously been prescribed an oral contraceptive within the last 3 years from the date of an original medical practitioner's prescription.

We seek confirmation that as written, any woman who has previously been prescribed any oral contraceptive by a medical practitioner in the previous 3 years could receive any (of the reclassified) oral contraceptives by an approved pharmacist. Meaning the pharmacist could switch between different products and active ingredients.

Or does the committee intend an activity related to a repeat dispensing of the same medication as prescribed? That is, more of a continuation of supply of the same oral contraceptive?

We also ask why a 3-year timeframe was chosen for the time from previous prescribing by a medical practitioner? We would be interested in the reason this time was chosen as pharmacists will need to track the previous prescriber to confirm details of what was previously prescribed. A three-year window presents the chance that a woman may stop her contraceptive, fall pregnant and have a child, then seek return to an oral contraceptive.

6 SUBMISSIONS FOR RECLASSIFICATION

6.1 Alcohol >20% - proposed extension of the general sales medicine classification of alcohol >20% to have the additional requirement of the product being wall mounted.

The Society is unclear about what this proposal applies to or indeed its purpose. The classification of alcohol in medicines containing more than 20% as general sale does not describe any specific form of medicine. While we're not aware of specific products that this proposal may apply to that are not handsanitisers, the proposal would set the additional requirement for all forms of alcohol >20% that are medicines to be wall mounted. We would also seek clarity from the committee or Medsafe that handsanitisation is considered a therapeutic purpose and therefore handsanitisers are classified as medicines?

The proposal does not present convincing evidence, or in fact a stated reason why these products should be wall mounted. As the classification applies to all medicines containing alcohol >20% and not specifically handsanitisers, we therefore would **oppose** the proposed classification.

6.2 Adapalene – proposed reclassification from prescription medicine to prescription medicine except in medicines containing not more than 1 mg/g and when supplied in a pack of not more than 30 g by a pharmacist.

The Society **strongly supports** the proposal to down-schedule adapalene from prescription medicine to permit supply by a pharmacist without a prescription. We understand from the proposal that the manufacturer will not be able to provide NZ-specific non-prescription packaging. Despite this, the Society would also support the reclassification to restricted medicine status.

New Zealand pharmacists are very familiar and experienced with managing mild-moderate acne over the counter, advising on self-management and non-pharmacological management, as well as advising on pharmacological treatments available without a prescription. The proposal seeks use in mild-moderate acne, which The Society considers pharmacists are already competent to assess and manage this, and can determine a greater level of severity that would require medical referral.

The Society considers that pharmacists are very well placed to supply adapalene without a prescription, safely and appropriately, and with guidance to the specific use of adapalene and its place in therapy, this would be managed well. We do not see a need for specific training or protocols to be complied with to enable supply, however the Society would develop guidance for the supply of adapalene by pharmacists, as we provide similar levels of guidance for other specific pharmacist-only medicines.

The Society supports the evidence and case presented for the reclassification of adapalene and this proposal has our full support.

6.3 Albendazole – proposed reclassification from prescription to pharmacy-only medicine (Te Arai BioFarma Ltd)

The Society has reservations about the classification of albendazole as a pharmacy-only medicine. The proposal presents valid evidence of the safety and efficacy of albendazole; and the history of safe and appropriate supply of mebendazole over the counter certainly supports a pharmacy-only classification.

While the Society supports that the safety profile of albendazole is likely to be similar to the existing mebendazole that is available through pharmacy, we would seek greater clarity around albendazole's place in therapy and how pharmacists might determine when use of albendazole might take preference over mebendazole or whether both should "just be available". The proposal asks to make albendazole available as an alternative anthelmintic "particularly when resistance is a concern". We would like to see greater evidence of the assessment of resistant infestations and the management of these in pharmacies if this is a particular therapeutic difference, in order to determine whether this would be considered appropriate. However we would suggest such a practice would not be consistent with good antimicrobial stewardship.

6.4 Loratadine – proposed extension of the current general sales classification to include an increased pack size (Claratyne 10 mg tablets, Bayer Healthcare Ltd)

The Society **opposes** the proposal to extend the current general sales classification of loratadine to include an increased pack size.

The intent of making smaller pack sizes of medicines available as general sale is to restrict use to short-term management of simple symptoms that a layperson would be expected to self-diagnose and self-manage. However with prolonged self-treatment, there is a risk that the self-diagnosis is incorrect, the medicine is ineffective or suboptimal, or the person may delay seeking professional opinion which might offer a more effective product that may be more cost-effective in resolving symptoms quicker.

6.5 Change in classification wording of lansoprazole, promethazine, sumatriptan, ibuprofen, omeprazole, pantoprazole, opium, pholcodine and ranitidine – proposed change in classification wording (Pharmaceutical Society of New Zealand)

This is a submission The Society has made to the committee that we intend appear before the committee to discuss further.

8.2 Decisions by the Secretary to the Department of Health and Aging in Australia (or the Secretary's Delegate)

8.2.1 Decisions by the Delegate – November 2015
Decisions also included under agenda item 8.1.
d) Naloxone

We note the decision by the delegate to reschedule naloxone to restricted medicine (Schedule 3) when used for the treatment of opioid overdose. Naloxone is currently classified as a prescription medicine in New Zealand and we would support any consideration to harmonise the medicine classification with Australia.

The arguments in Australia for rescheduling also apply to New Zealand. While we cannot state what the potential market might be, having naloxone available without a prescription would support the reduction of risk of harm around the misuse of opioids. The Society notes the role of pharmacies across New Zealand in participating in the Needle Exchange Programme to support risk reduction in people who inject drugs. The Pharmaceutical Society is an active supporter and stakeholder of the needle exchange programme, and the facility to provide naloxone over the counter alongside needles and syringes would be an ideal avenue.

The Society would support such a reclassification in New Zealand by ensuring a training programme on the use and supply of naloxone were available to the profession. We would be please to discuss this further with the Committee should a reclassification be considered in New Zealand.

Thank you for consideration of this submission.

Yours sincerely,

Bob Buckham BPharm, PGCertPharm, PGDipClinPharm, MPS, ANZCP, RegPharmNZ
Chief Pharmacist Advisor

PHARMACY GUILD OF NEW ZEALAND

05 April 2016

Advisor Science (Secretariat for MAAC & MCC)

Product Regulation

Medsafe

Sent via email to: committees@moh.govt.nz

Dear Medicines Classification Committee

RE: AGENDA FOR THE 55th MEETING OF THE MEDICINES CLASSIFICATION COMMITTEE

Thank you for making available the agenda for the 55th meeting of the Medicines Classification Committee (MCC), to be held on Tuesday 3 May 2016, and for the opportunity to provide feedback on the agenda.

The Pharmacy Guild of New Zealand (Inc.) (the Guild) is a national membership organisation representing the majority of community pharmacy owners. We provide leadership on all issues affecting the sector.

Our feedback covers nine agenda items. These are:

- Agenda item 5.1.1: Oral contraceptives – objection to the proposed reclassification from prescription medicine to restricted medicine (Royal New Zealand College of General Practitioners).
- Agenda item 5.2.1: Updating the guidance document titled 'How to change the legal classification of a medicine in New Zealand' to include the publication of additional information submitted in objections.
- Agenda item 5.2.4: Change in classification wording of benzydamine – change in classification wording of benzydamine from general sales medicine for topical and external use to general sale medicine for oral mucosal and topical use.
- Agenda item: 5.2.5: Classification wording of lignocaine – proposed amendment to classification wording.
- Agenda item 6.2: Adapalene – proposed reclassification from prescription medicine to prescription medicine except in medicine containing not more than 1mg/g and when supplied in a pack of not more than 30 g by a pharmacist (Green Cross Healthcare Ltd and Natalie Gauld Ltd).
- Agenda item 6.3: Albendazole – proposed reclassification from prescription to pharmacy-only medicine (Te Arai BioFarma Ltd).

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- Agenda item 6.4: Loratadine – proposed extension of the current general sales classification to include an increased pack size (Claratyne 10 mg tablets, Bayer Healthcare Ltd).
- Agenda item 6.5: Change in classification wording of lansoprazole, promethazine, sumatriptan, ibuprofen, omeprazole, pantoprazole, opium, pholcodine and ranitidine – proposed change in classification wording (Pharmaceutical Society of New Zealand).
- Agenda item 8.2.1: Decisions by the Delegate – November 2015; Esomeprazole, hydrocortisone, levocetirizine and naloxone.

Each of these agenda items are discussed below.

Agenda item 5.1.1: Oral contraceptives – objection to the proposed reclassification from prescription medicine to restricted medicine (Royal New Zealand College of General Practitioners)

The Guild **agrees** that the alternative proposal submitted by Green Cross Healthcare should have been made publically available, so that all the relevant stakeholders had the opportunity to respond.

The Guild's view on the reclassification of oral contraceptives remains unchanged. We are **strongly supportive** of the reclassification of oral contraceptives from prescription medicine to restricted medicine. We agree with this classification, whether for supply to women who have previously had an oral contraceptive prescribed or for women who have not. Supplying the oral contraceptive to women who have not been previously prescribed an oral contraceptive before, when they are requesting an emergency contraceptive pill for example, alongside referral to a medical practitioner or family planning clinic provides greater protection against pregnancy than repeat use of the emergency contraceptive pill.

As outlined in our previous oral contraceptive reclassification submission in the 53rd Medicine Classification Committee meeting; we see this as a positive step towards a collaborative healthcare framework. Better utilising the pharmacist in the workforce through task-shifting can alleviate some of the daily pressures faced in general practice. Pharmacists are well trained and well placed to provide many healthcare services. Being able to receive the oral contraceptive directly from a pharmacist will improve access for many women.

Our expectation is that practicing pharmacists would ensure they are competent to provide the oral contraceptive and would undertake self directed training to ensure such competence still stands. However, we accept the committee's decision to mandate training if this was preferred.

We note the increased availability of the contraceptive pill through pharmacists in States in the USA, most Canadian provinces, and the United Kingdom. We believe New Zealand women should be able to share the advantages of this international trend.

Agenda item 5.2.1: Updating the guidance document titled 'How to change the legal classification of a medicine in New Zealand' to include the publication of additional information submitted in objections

As stated above in agenda item 5.1.1 we believe all the relevant stakeholders should be made aware of, and have the opportunity to respond to, any alternative proposals before the MCC makes a decision on the reclassification of any medicine. We believe it would be helpful in future instances to know any alternative options proposed as part of an objection and we agree that the guidance document needs to reflect this.

Agenda item 5.2.4: Change in classification wording of benzydamine – change in classification wording of benzydamine from general sales medicine for topical and external use to general sale medicine for oral mucosal and topical use

The Guild is **opposed** to MedSafe's decision to amend the wording of the classification of benzydamine. While we understand MedSafe was incorporating what the MCC was trying to capture in its recommendation following the 54th meeting we feel there are good reasons to leave the classification as it was.

The change in the wording of benzydamine classification from "General sale; for dermal use" to "General sales medicine; for oral mucosal or topical use" allows more products that alleviate the symptoms of a sore throat to be available to consumers without advice from a trained healthcare professional. This decision is not in line with the government's strategy for rheumatic fever prevention.

Currently many parents and caregivers take their children with sore throats to a pharmacy to get advice and treatment. If the pharmacist suspects the child might have a streptococcal throat infection the pharmacist then makes a prompt referral to a doctor. In some high risk areas the pharmacist is able to provide appropriate management for suspected streptococcal infection. These provisions allow for early detection and treatment, which reduces the child's risk of developing rheumatic fever. We believe this amendment poses the risk that children with a potential streptococcal throat infection will be bypassing important health professional advice, which will increase their chances of developing rheumatic fever.

Rheumatic fever in New Zealand demonstrates an extreme health disparity, where the prevalence is much higher among Maori and Pacific Island children. We believe this amendment has the risk of further increasing rheumatic fever related health disparities.

Agenda item: 5.2.5: Classification wording of lignocaine – proposed amendment to classification wording

The Guild is **opposed** to the proposed wording amendment to the classification of lignocaine. The inclusion of throat sprays in this wording would increase the number of products available for consumers to manage a sore throat without advice from a trained heath professional. Our reasons for opposing this are outlined in agenda item 5.2.4 (above).

Agenda item 6.2: Adapalene – proposed reclassification from prescription medicine to prescription medicine except in medicine containing not more than 1mg/g and when supplied in a pack of not more than 30 g by a pharmacist (Green Cross Healthcare Ltd and Natalie Gauld Ltd)

The Guild **strongly supports** the proposed reclassification of adapalene from prescription medicine to prescription medicine except in medicine containing not more than 1mg/g and when supplied in a pack of not more than 30 g by a pharmacist.

We agree with Green Cross Healthcare that currently there is a gap in the non-prescription market for acne treatment. This has been the case since topical clindamycin was reclassified as prescription only in 2002. We believe adapalene is a suitable product to fill this gap.

Topical retinoids, such as adapalene are recommended as first line treatment for mild to moderate acne. Acne is a common condition, and in most instances acne is self-diagnosed and self-treated, but can be considered a chronic and debilitating condition in many cases. The physical and emotional effects from acne can last a lifetime. Acne has been shown to be associated with depression, anxiety, low self-esteem and suicide, and can impact on an individual's ability to gain employment [(1)]. Early intervention for acne can provide optimal treatment outcomes that can positively influence an individual's life course. We believe making adapalene available through a pharmacist would allow acne sufferers to commence on a first-line treatment sooner, and provide a pathway in more severe cases for early referral to a doctor.

There are known barriers for accessing acne treatment in New Zealand [(2)]. Previously access to funded oral isotretinoin for acne was only available from a dermatologist due to concerns surrounding its safety. It was only in recent years that funded isotretinoin treatment became available through general practitioners to improve access for acne treatment. While this has improved access for many New Zealanders we understand barriers still exist. This could be because many people who suffer from acne do not believe it is something they need to consult a doctor about, or are unware that there are effective treatments available that will make a sufficient difference for them. Pharmacists are accessible and are ideally placed in the community, and already provide consumers with advice on over-the-counter and prescribed acne treatments. We strongly believe enabling adapalene to be available from a pharmacist would reduce current barriers to accessing acne treatment.

We are aware that some stakeholders might have concerns surrounding the use of adapalene in women of child-bearing age due to the theoretical teratogenic risks. The systemic absorption of topical adapalene is extremely low, and both adapalene products available in New Zealand have explicit warnings about their risks during pregnancy on the packaging and consumer information sheets. Tretinoin is another topical retinoid that was classified as a pharmacist-only medicine in New Zealand until the early 1990s. It was reclassified as a prescription only medicine because the packaging did not include any warnings about risks during pregnancy. Plenty of other medications that are contraindicated or not recommended in pregnancy are available over-the-counter (eg, NSAIDs). Pharmacists are well aware of these medicines and warn against use of specific medicines in pregnancy, and ask about possible pregnancy on a regular basis. Given that adapalene is a topical medicine we think it is even more important to get this message

across, as we believe consumers may not be aware of contraindications of topical medicines in pregnancy the way they are with oral medicines.

We understand that adapalene has recently been considered for reclassification in Germany [3], and in the past has been considered for reclassification in the United Kingdom [4]. It is important to note that neither of these jurisdictions have a Pharmacist-Only medicine classification. Having a Pharmacist-Only classification ensures medicines that are classified as such are sold by a registered pharmacist. The reclassification of adapalene in New Zealand would require a pharmacist to be involved in every sale, which might not be the case in Germany or the United Kingdom.

We believe that New Zealand pharmacists are capable of recommending and providing acne treatment, and counselling their patients on the appropriate use of adapalene, as well as advising female patients about the risks during pregnancy. It is our expectation that the supply of adapalene through pharmacists would use the Pharmacy Council Protocol for the Sale and Supply of Pharmacist only Medicines for a Chronic Condition. This includes a provision for referral to and consultation with other health practitioners caring for the person where appropriate. The Guild will also put out clear messages to our members about needing to avoid adapalene use during pregnancy, and to reinforce this message with a further warning on the dispensing label.

Pharmacies are often the first place consumers' visit to obtain advice and products to treat acne, and as such we support the proposed reclassification of adapalene. This will allow patients to have access to a first-line acne treatment, so they can commence an effective treatment earlier. We believe this will have flow on benefits for their emotional and psychological health.

Agenda item 6.3: Albendazole – proposed reclassification from prescription to pharmacy-only medicine (Te Arai BioFarma Ltd)

The Guild is **opposed** to the proposed reclassification of albendazole from prescription to pharmacy-only medicine.

Currently the only products of albendazole available in New Zealand are section 29. This means MedSafe has not assessed them for their safety or efficacy. Alendazole is indicated for the treatment of hydatid disease (echinococcosis); hookworms; cutaneous larva migrans; strongyloidiasis [5]. These infections are not common in New Zealand, and we therefore do not see a suitable demand to justify this reclassification. Given that these infections can be acquired after visiting a developing country we believe it is more suitable for a patient to be reviewed by their doctor in case of other potential health concerns from travelling in these sorts of areas.

We noted, and are concerned that the pregnancy category for albendazole is D [5]. This means albendazole has been identified as having an increased risk for causing human foetal malformations [5]. In New Zealand mebendazole and pyrantel are used to treat threadworms, a common childhood infection. These products are available as Pharmacy-Only Medicines in New Zealand, but their associated risk in pregnancy is deemed much lower than albendazole. While pharmacists are responsible for the sale of Pharmacy-Only medicines in their pharmacy this classification does not ensure the product is sold by a

pharmacist, and we believe a Restricted Medicine classification is more suitable for products with such risks.

Our concerns regarding the safe use of albendazole make us believe that a Pharmacy-Only classification is not a suitable for this medicine.

Agenda item 6.4: Loratadine – proposed extension of the current general sales classification to include an increased pack size (Claratyne 10 mg tablets, Bayer Healthcare Ltd)

The Guild **strongly opposes** the proposed extension of the current general sales classification of loratadine to include an increased pack size.

We believe that increasing the available pack size of loratadine by general sale poses several risks to the consumer. Increasing the available pack size of loratadine from five tablets to 10 tablets would provide consumers with 10 days supply of the medicine. Paracetamol and ibuprofen are examples of other medicines that are available through general sale. We would like to point out that the quantities of these medicines are only sufficient to provide therapeutic dosing for less than five days. We believe that 10 days supply of any medicine is excessive in the absence of advice from a healthcare professional, and increases the risk of the consumer's health deteriorating further, potential side effects, drug interactions and unintended overdoses.

We are concerned in the absence of professional healthcare advice consumers will be unable to make an informed choice about the treatment options best suited to treat their seasonal allergic rhinitis. Loratadine is also used to treat a range of allergic disorders [(6)] [(7)]. We are concerned that the general consumer is unable to differentiate between seasonal allergic rhinitis and other allergic disorders that require advice from a health professional, and that infections can sometimes be incorrectly self-diagnosed as an allergy.

We are concerned that with general sales, consumers will not be made fully aware of any potential side effects from loratadine. Like other medicines loratadine has side effects, and it is important that consumers are aware of these side effects so they know when to seek help. Headache, sedation, fatigue and dry mouth are commonly reported side effects of loratadine [(7)]. Rare but more severe side effects such as; hypotension, palpitation, arrhythmia, extrapyramidal effects, dizziness, confusion, depression, sleep disturbances, tremor, convulsions, hypersensitivity reactions (including bronchospasm, angioedema, anaphylaxis, rash photosensitivity reactions), blood disorders, liver dysfunction, and angle-closure glaucoma have also been reported [(7)]. There have also been case reports of QT prolongation, which can have fatal consequences, following therapeutic doses of loratadine [(6)].

Loratadine should be used with caution in people with hepatic impairment [(7)], and has the potential to interact with other medicines [(7)]. We believe in the absence of health professional advice larger packs sizes put people are at greater risk of potential drug interactions.

We are concerned that increasing the available pack size of loratadine through general sale would increase the number of unintended loratadine overdoses. Health professionals

play an important role in preventing medicine overdoses, as they are able to verbally advise and reinforce the recommended doses to consumers. The National Poisons Centre has advised us that over an eight year period (1 January 2008 to 31 December 2015) they received 561 calls relating to potential loratadine overdoses. Of these calls only 58 were intentional overdoses.

Consumers are already able to purchase five days of supply of loratadine without any health care advice. For the reasons highlighted above this is a more than sufficient quantity. We believe that increasing the pack size of loratadine available through general sale has the potential to be a risk to public safety, and result in poor patient outcomes.

Agenda item 6.5: Change in classification wording of lansoprazole, promethazine, sumatriptan, ibuprofen, omeprazole, pantoprazole, opium, pholcodine and ranitidine – proposed change in classification wording (Pharmaceutical Society of New Zealand)

The Guild is **strongly supportive** of the Pharmaceutical Society of New Zealand's (the Society) proposal for the change in classification wording of lansoprazole, promethazine, sumatriptan, ibuprofen, omeprazole, pantoprazole, opium, pholcodine and ranitidine to enable pharmacists to repackage already approved over-the-counter products into smaller quantities when appropriate. We believe this amendment would reflect what we consider acceptable and professional practice.

We receive many enquires from our members asking if they can repackage pharmacy only or pharmacist only medicines into smaller packs, as this is often requested by their customers. Regulation 23 of the Medicine Regulations enables pharmacists to repackage medicines provided the product meets specific labelling requirements, and is not advertised or stocked on the shelf for consumer self-selection. Currently not all Restricted or Pharmacy-Only Medicines are required to be sold in approved or manufacturer's original packs. However, for the medicines included in this agenda item the classification wording states these medicines can only be sold in approved or manufacturer's original packs.

For many patients having the choice to obtain over-the-counter medicines in smaller quantities is often more affordable and convenient. This can also allow for course specific quantities to be supplied that will minimise medicine wastage, and the likelihood of unused medicines being stored at home and used by other family members. The current wording in the classification of lansoprazole, promethazine, sumatriptan, ibuprofen, omeprazole, pantoprazole, opium (Gee's Linctus), pholcodine and ranitidine limits pharmacists' ability to meet their patients' needs. These medicines have already been approved for the supply from a pharmacist or pharmacy, but some of these medicines do not have approved over-the-counter packaging available. This means the pharmacist is unable to supply them to meet patient need.

Pharmacists are trained health professionals who are able to ensure the appropriate use of medicines. We do not envisage any risk to the public by changing wording on the classification of these medicines, as a pharmacist would be involved in the recommendation and the supply of these medicines. Enabling pharmacists to supply these medicines in smaller quantities can address concerns around potential drug misuse eg Gee's Linctus. The removal of the requirement for only using approved packs can also

allow a trial course where that is appropriate (eg with the Proton pump inhibitors) and/or reduce cost related barriers for patients who only want a few doses of eg, ibuprofen. Repacking and supplying medicines in smaller quantities enables pharmacists to issue the product with a named patient label. This is likely to reduce the chances of the medicine being shared with other people for whom the medicine was not intended.

Some pharmacies might not stock the approved over-the-counter pack for a particular medicine where the demand for that product might be very low in their area; however the pharmacy is likely to have a larger 'dispensing' pack available. If the wording in the classification for these medicines was changed this would enable pharmacists to meet these "one off" requests from a customer eg sumatriptan, and would also facilitate the supply of a needed medicine in the event of a stock out of a proprietary product.

We believe the change is this classification would provide better patient outcomes. Currently the proton pump inhibitors (PPIs) omeprazole, pantoprazole and lansoprazole are all classified as over-the-counter products, but only omeprazole products are available in approved packaging. Changing the wording of the classification would allow patients to easily try different PPI to determine which one is more effective for alleviating their symptoms.

The cost of many of the approved proprietary products currently available can act as a barrier in low socioeconomic areas. We believe enabling pharmacists to repackage these medicines will allow more affordable options for patients who have cost constraints for accessing healthcare eg, liquid ibuprofen.

Changing the wording of classification will not change the requirements of supply of these medicines, and any indication, age restriction, maximum dose size or quantity would still apply. Should the Society's proposal be accepted we would ensure our members are well aware of their legislative obligations, and ensure supply is done safely and appropriately and in accordance with any contraindications, precautions or other safety information that is related to particular medicines.

We are in strong support of the Society's proposal. Allowing pharmacists to repackage medicines that can already be sold over-the-counter into smaller quantities offers many benefits to the public, and does not compromise patient safety.

Agenda item 8.2.1: Decisions by the Delegate

a) Esomeprazole

The Guild is **strongly supportive** of the reclassification of esomeprazole from prescription medicine to either Restricted or Pharmacy-Only Medicine to facilitate the harmonisation between New Zealand and Australian schedules.

Allowing esomeprazole to be available over-the-counter in New Zealand would allow for more patient choice. As mentioned in agenda item 6.5; this would facilitate the trail of another PPI that might be better in managing particular patients' symptoms.

b) Hydrocortisone

The Guild is **opposed** of the reclassification of any products containing 1% of hydrocortisone from Restricted-Only to Pharmacy-Only Medicine, even if it is to facilitate the harmonisation between New Zealand and Australian schedules.

Combination products containing 1% of Hydrocortisone and an antifungal are currently classified as Restricted-Only Medicines in New Zealand. We believe this classification should remain to protect patient safety. Pharmacists play an important role in assessing minor skin infections. It is not uncommon for pharmacists to pick up skin cancers and refer these on to a GP or skin specialist. Many of the skin infections presented to pharmacists are bacterial and require referral to a doctor. We would not like to see instances where a patient continued to treat a sore that didn't heal with one cream after another before giving up and asking for advice.

We believe changes to this classification could break down the established referral pathway, and have consequences on patient health outcomes.

c) Levocetirizine

The Guild is **supportive** of the harmonisation between New Zealand and Australian schedules, and notes that levocetirizine is already classified as a Pharmacy-Only Medicine in New Zealand.

d) Naloxone

The Guild is **supportive** of the reclassification of naloxone from Prescription-Only to Restricted Medicine to facilitate the harmonisation between New Zealand and Australian schedules.

Naloxone is used in the treatment of opioid overdose. In New Zealand the majority of people who experience an opiate overdose would present at an emergency department, but supply from a pharmacy could result in quicker treatment and better outcomes for some. We imagine the demand for over-the-counter naloxone in New Zealand would be extremely low. If the reclassification of naloxone took place, for the reasons mentioned in agenda item 6.5, it would be important to ensure pharmacists are able to repackage this product.

Thank you for considering our feedback. If you have any questions about our feedback, please contact our Guild Pharmacist, Professional Services and Support, Sarah Bannerman at s.bannerman@pgnz.org.nz or 04 802 8209.

Yours sincerely,

Linda Caddick
Professional Services and Support Manager

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The Royal New Zealand
College of General Practitioners
Te Whare Tohu Rata o Aotearoa

5 April 2016 Our Ref: HMB38-16

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Dear Hannah

Thank you for the opportunity to comment on the agenda of the 55th meeting of the Medicines Classification Committee (MCC) of Medsafe.

Executive summary

The RNZCGP considers that in order to support robust decision making, the processes used by the MCC should be modified to be more transparent and consultative. The College has commented on a number of other items on the agenda of the 55th meeting, including the reclassification of selected oral contraceptives (desogestrel, ethinylestradiol, norethisterone and levonorgestrel).

General practice and the College

General practice is the range of values, knowledge, skills, and practices required to provide first level medical services in both community practice and hospital settings. General practice includes the provision of both first contact and continuing care for all ages and both sexes that is comprehensive, person-centred, and takes into account the roles of family, whānau, community and equity in achieving health gains.

GPs comprise almost 40 per cent of New Zealand's specialist workforce and their professional body, the Royal New Zealand College of General Practitioners (the College), is the largest medical College in the country. The College provides training and ongoing professional development for GPs and rural hospital generalists, and sets standards for general practice. The College is committed to:

- Ensuring that New Zealand has a GP workforce that contains sufficient vocationally trained GPs to: ensure appropriate service provision; enable sustainable, safe, high quality primary health care; meet the increased demands of an ageing population and higher rates of co-morbidity; and to meet the Government's expectations of care that is sooner, better and more convenient.

- Improving patient outcomes with regard to continuity and access to quality care by: promoting better integration between primary care, secondary care and social service; and encouraging innovation and the development of new models of care.

- Achieving health equity in New Zealand through: a greater focus on the social determinants of health; reducing the rates of smoking and increasing health food options for low-income families; better integration of health and social services; and ensuring that funding for primary care is targeted to the most disadvantaged.

- Improving health outcomes for rural communities through the work of high quality, well trained medical generalists working within multidisciplinary teams.

- Achieving health equity for Maori. Health equity for Māori will be achieved when Māori have the same health outcomes as other New Zealanders. For this to occur, service delivery to Māori needs to be appropriate and effective and ensure equity of access. This does not mean a reduction in service delivery to other New Zealanders, but rather improving service delivery to Māori to ensure fairness.

The College's response

The items on the agenda for the 55th meeting on which the College would like to comment are:

- Item 5.1 Objections to recommendations made to the 54th meeting
- Item 5.1.1 Oral contraceptives
- Item 5.2.1 Updating the guidance document
- Item 5.2.3 Review of tramadol and codeine reclassification
- Item 6.2 Adapalene
- Item 6.3 Albendazole
- Item 8.2.1 Naloxone

MCC processes (Items 5.1 & 5.2.1)

The College considers that the MCC needs to implement a consultation process that is:

- Proactive, where all interested parties are identified and actively invited to comment on issues
- Open and where full information is provided when comment is being sought, including key details of protocols to be used
- Coherent where information is provided in plain English and in a form that can easily be accessed and digested
- Robust with safeguards to prevent regulatory capture included such as seeking input from clinical groups directly, rather than relying on industry to do so

In February 2016 the College objected to the process used in relation to agenda item 5.1.1 (oral contraceptive pill) for the 54th meeting. An item on this matter was then included in the 55th meeting agenda (item 5.2.1).

The College's letter outlining its concerns and the grounds for its objection is publically available on the medsafe website[1]. We consider it appropriate that the grounds for any objection are made public as this enables stakeholders to comment on the matter from their perspectives, which is important for informed decision making. The grounds for objection may be sufficient to be considered "valid" for the purposes of triggering further consideration of the item by the committee, however that does not mean that it should be an in committee discussion or that stakeholders should not have the opportunity to counter the arguments made by the objecting organisation. The College would have provided an alternative opinion and disputed a number of the statements made had it been given the opportunity to do so.

[1] http://www.medsafe.govt.nz/profs/class/Agendas/agen55OralContraceptivesCollegeofGPs.pdf

We are very concerned that despite emailing the MCC secretariat in August 2015 requesting information on the grounds on which the objection had been made, they did not provide us with this information. We remained unaware of the grounds on which an objection had been made until the minutes of the 54th meeting held in November 2015 were made public in January 2016.

It is pleasing that the grounds for the RNZCGP's objection were made publically available, and we consider that in future the basis for objections should likewise be made available for scrutiny.

Our second objection also relates to the availability of information for agenda item 5.1.1 of the 54th meeting. The alternative proposal put forward by Green Cross to the 54th meeting was not made available for comment prior to the meeting. However the Committee thought that it had been publicised and therefore went ahead and debated it. Consequently the College and other stakeholders were not able to consider this proposal and provide feedback on it.

Further comments regarding MCC processes and the guidance document.

The benefits of information and the costs of commercial sensitivity

Recent years have seen the introduction of schedule changes where medications remain prescription-only "except where supplied by a registered pharmacist who has successfully completed additional training in..."

The detailed circumstances in which patients can be supplied medications (e.g. which age groups) and the absolute and relative contraindications to supply, are sometimes contained in the wording of the submission itself and hence are publically available. In other cases however, only some of these are made publically available and others are contained in a checklist that is kept secret on the grounds of commercial sensitivity. This secrecy has a number of negative consequences.

Without access to this information GPs remain concerned about the safety of pharmacist supply. Making this information available when proposals are consulted on, would enable GPs to assess the safety of the service proposed and in many cases would enable them to be reassured.

Such information would assist GPs in advising their patients whether or not they are suitable candidates to be supplied with a medication by a pharmacist in future. In addition it would assist in enhancing the collegiality between pharmacists and general practitioners.

Health practitioners are accustomed to cooperating with each other in the care of patients and sharing information in the interests of promoting best practice. The secrecy that is seen in some of the applications to the MCC, around which patients may be eligible for supply by a pharmacist, is counterproductive, foreign and unwelcome in the healthcare environment. Making items such as checklists available for public consultation will also assist in identifying improvements that could be made.

The College is aware of the considerable resource required to develop a training programme. It is reasonable that the training programme itself is considered commercially sensitive. This should not extend to information about the criteria on which decisions whether supply of a medication are based.

The document *Guidance On How To Change The Legal Classification Of A Medicine In New Zealand*[2] includes on page 6 a list of what is required to be included in a submission for reclassification (see Appendix 1).

[2] http://www.medsafe.govt.nz/downloads/How_to_change_medicine_classification.pdf

One item on the list is "Pack size and other qualifications". The College would like to suggest that providing information on "other qualifications" should become a requirement in its own right. The information provided under this heading should include a list of the circumstances under which the medication can and cannot be supplied including the absolute and relative contraindications. This information may be presented in the form of a checklist or protocol.

Fragmentation of care

Any rescheduling of a prescription medicine will create some level of fragmentation of care; hence 'an increase in fragmentation' is inappropriate as an absolute block to rescheduling. This is not what the College intended when it argued for the inclusion of 'fragmentation of care' in the classification criteria in its response to the agenda of the 50th meeting of the MCC in 2013.[3]

The degree and potential consequences of fragmentation of care vary greatly among the reclassification proposals put to the committee. For some medications, where there is a strong link between the prescription of that medication and the provision of other services, the consequences of fragmentation of care present a risk to patients. The College considers that taking a narrow view of relevant criteria for a decision on reclassification is not in the interests of the public. If the MCC constrains itself to considering only some of the consequences of schedule changes, proposals recommended by the MCC should be required to also then be considered by a body with a broader view.

Item 5.1.1 Oral contraceptives

The agenda item reads:

> *"The Committee's recommendation of reclassifying selected oral contraceptives (desogestrel, ethinylestradiol, norethisterone and levonorgestrel) from prescription medicine to restricted medicine, when sold in the manufacturer's original pack containing not more than six months' supply by a registered pharmacist who has successfully completed a training programme, when indicated for oral contraception in women who have previously been prescribed an oral contraceptive within the last 3 years from the date of an original medical practitioner's prescription."*

The College wishes to reiterate that it strongly supports the ready availability of safe, effective, and acceptable contraception. Our major dispute is with the process that was followed and the precedent it creates for future decision making. As for the decision reached regarding the oral contraceptive pill (OCP) we have only minor changes to suggest.

The College remains opposed to the supply of the OCP without prescription to women who have not previously been prescribed it. The reasons for this have been outlined in the Colleges previous submissions to the MCC in response to the agendas of the 51st and 53rd meetings of the MCC.[4] [5]

However, the College would be supportive of the alternative proposal from Green Cross with some minor modifications. We would have liked to have had the opportunity to raise these issues in a response to the agenda of the 54th meeting. If we had been provided with the information to enable this prior to the meeting, then the delay in progressing pharmacist supply of the OCP in appropriate situations (arising from the need for this issue to be reconsidered by the committee), could have been avoided. The precedent set by the process used must be challenged so that future decisions are made in the public's interest rather than the industry's.

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[3] https://www.rnzcgp.org.nz/assets/documents/Sumbissions/50th-meeting-of-medicines-classification.pdf

[4] http://www.medsafe.govt.nz/profs/class/Agendas/agen51CommentsOnSubmissions.pdf p30

[5] http://www.medsafe.govt.nz/profs/class/Agendas/agen53comments.pdf p 70

The College considers a repeat supply of a woman's OCP without prescription is reasonable provided that before dispensing, the pharmacist ensures that there has not been a change in the woman's health (or that of her close relatives), that would indicate that she should be advised that the OCP may no longer be the best contraceptive option for her. Additionally the woman should:

- have been prescribed that OCP within the past year
- have been reviewed by an authorised prescriber at least once since starting the OCP for the first time

This differs slightly from the "alternative proposal" put forward by Green Cross at the 54th meeting in that:

- the interval between prescriptions has been reduced from 3 years to 1 year
- a requirement is added that for woman receiving the OCP for the first time (OCP naïve), one follow up appointment with an authorised prescriber is required before further repeats can be provided without prescription.

RNZCGP members considered that an interval of three years between prescriptions is too long and should be shortened, ideally to one year. This would minimise many of the issues around the difference in the level of holistic and comprehensive care that can be provided to the woman by her general practice team, as opposed to what can be provided by a pharmacist in a pharmacy setting.

Reducing the interval between prescriptions from 3 years to 1 year would also would address issues with repeat prescriptions in older women. The submission document does not state the age beyond which supply without prescription will not be permitted. We consider that this is a significant omission.

In relation to the upper age limit for the COCP we draw you attention to a recent case highlighted by the Medical Protection Society in which the complainant suffered a stroke. Expert opinion was that a reasonably competent GP would have stopped prescribing the OCP to a woman with her history at the age of 35.[6] The checklist that we were shown by Green Cross in February 2015 had an upper age limit higher than this, although it did also contain advice regarding use in this age group.

We were permitted to share this check list with a small number of GPs. They expressed concerns about some of the content. In our response to the 53rd agenda we commented that, "If the check-lists are to be used, we would expect the College to be further consulted before implementation". There is a need for this information to be made publically available and reviewed.

Item 5.2.3 Review of tramadol and codeine reclassification

The agenda item reads:

> *"The Committee will review the outcomes of the Australian Advisory Committee on Medicines Scheduling meeting to take place 15-17 March 2016."*

There is no further information provided on what is being proposed at the Australian Advisory Committee on Medicines Scheduling meeting. Information on the outcome of the meeting has not been provided. The college is concerned that it is not possible to comment on this agenda item without this detail.

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[6] http://www.medicalprotection.org/docs/default-source/pdfs/casebook-pdfs/new-zealand-casebook-pdfs/nz_book_web.pdf?sfvrsn=6 p13

Item 6.2 Adapalene

The agenda item for Adapalene reads:

> *"Proposed reclassification from prescription medicine to prescription medicine except in medicines containing not more than 1 mg/g and when supplied in a pack of not more than 30 g by a pharmacist (Green Cross Healthcare Ltd and Natalie Gauld Ltd)*
>
> *This is a submission (PDF 2.54 MB, 20 pages) to reclassify adapalene from prescription medicine to prescription medicine except in medicines containing not more than 1 mg/g and when supplied in a pack of not more than 30 g by a pharmacist for the topical treatment of comedo, papular and pustular acne (acne vulgaris) of the face, chest or back."*

The College does not support the proposed reclassification on the following grounds:

Side effects

Members reported that in their experience, the adverse effects of Adapalene can be severe. The submission states:

> "Side effects of adapalene are primarily local skin effects. These side effects are not particularly different in nature to those occurring with benzoyl peroxide, a medicine commonly used in NZ with a general sales classification in some strengths".

While the side effects of both benzoyl peroxide and adapalene are similar in being primarily skin based, the magnitude of the side effects of adapalene should not be assumed to be comparable to the magnitude of the side effects of the general sale strength of benzoyl peroxide (5% or less), but rather the prescription strength (more than 10%).

Safety in pregnancy

Adapalene safety in pregnancy has not been established. There are reports of teratogenic effects in humans and teratogenicity is established in rodents. The NZ formulary states:

> "Topical retinoids are contra-indicated in pregnancy; women of child-bearing age must use effective contraception (oral progestogen-only contraceptives not considered effective)".[7]

The medsafe data sheet for Differin brand of Adapalene cream[8] includes mention of research showing "increased incidences of various naturally occurring skeletal variations were still observed following topical administration to rats". The data sheet concludes that:

> "Because of the risk of teratogenicity shown in animals, and since there are no adequately controlled studies in pregnant women, adapalene should not be used by women who are pregnant or who plan to become pregnant during treatment".

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[7] http://www.nzf.org.nz/nzf_6425

[8] http://www.medsafe.govt.nz/profs/datasheet/d/Differincrm.pdf

The submission states that pharmacists are aware of the importance of avoiding other non-prescription drugs in pregnancy, but does not state how this risk will be managed. The example given is of avoiding anti-inflammatories in the third trimester of pregnancy. Most women in the third trimester of pregnancy are visibly pregnant so pharmacist awareness would be high. A quite different approach is needed to avoid supplying contraindicated medication to women who are in early pregnancy or likely to become pregnant.

Shared medication and the need for examination

The risk of the medication being shared is increased when it is not obtained on prescription as patients are likely to perceive that there are no significant side effects.

An examination of the back and chest is required to establish the most appropriate management.

Missing information

The submission refers to additional information available in the appendices however these appendices are not included in the submission. The missing information is:

- Sales data (p4)
- Current labelling (p4)
- Consumer medicines information (p4)
- Datasheet (p9)
- Pharmacist only chronic use protocol (p14)
- SMARs report from medsafe (p16)

We suggest that the full submission should be made public and further comment sought.

Item 6.3 Albendazole

The agenda item for Albendazole reads:

> *"Albendazole – proposed reclassification from prescription to pharmacy-only medicine (Te Arai BioFarma Ltd)*
>
> *This is a company submission (PDF 2.39 MB, 75 pages) to reclassify albendazole from prescription medicine to pharmacy-only medicine in total doses not exceeding 400 mg for the treatment of a variety of parasitic worms."*

This proposal would allow Albendazole to be selected off the shelf in pharmacies without even the involvement of a pharmacist in the sale. The RNZCGP shares the concerns expressed by the Australasian Society for Infectious Diseases (ASID) in their submission to the MCC regarding the need for guidance to consumers, the risk in pregnancy, and the potential for worsening of resistance.

Item 8.2.1 Naloxone

The agenda item for Naloxone is under the heading of Decisions by the Secretary to the Department of Health and Aging in Australia (or the Secretary's Delegate). The College's understanding is that this relates to Trans-Tasman Scheduling Harmonisation[9]. The agenda item reads:

> *"A new restricted medicine (Schedule 3) entry should be created for naloxone when used for the treatment of opioid overdose."*

We note that in Australia Naloxone has recently been rescheduled and is now available without prescription. We wish to emphasise that this is only when Naloxone is to be used as part of a take home naloxone programme. These programmes involve training potential overdose witnesses in overdose response. The training includes - but is not limited to - naloxone administration.[10] Similar provisions and training are needed in New Zealand.

Concluding remarks

We hope you find our comments helpful. If you would like any further information or clarification please do not hesitate to contact the College's policy team (policy@rnzcgp.org.nz).

Yours sincerely

Helen Morgan-Banda
Chief Executive Officer

[9] http://www.medsafe.govt.nz/profs/class/harmon.asp
[10] https://www.mja.com.au/journal/2016/204/4/australia-reschedules-naloxone-opioid-overdose

Appendix 1

A submission for the reclassification of a medicine should include:

Part A

1. International Non-proprietary Name (or British Approved Name or US Adopted Name) of the medicine.
2. Proprietary name(s).
3. Name of the company / organisation / individual requesting a reclassification.
4. Dose form(s) and strength(s) for which a change is sought.
5. Pack size and other qualifications.
6. Indications for which change is sought.
7. Present classification of the medicine.
8. Classification sought.
9. Classification status in other countries (especially Australia, UK, USA, Canada).
10. Extent of usage in New Zealand and elsewhere (eg, sales volumes) and dates of original consent to distribute.
11. Labelling or draft labelling for the proposed new presentation(s).
12. Proposed warning statements if applicable.
13. Other products containing the same active ingredient(s) and which would be affected by the proposed change.

Part B Reasons for requesting classification change including benefit-risk analysis.

This section should be supported by the following:

1. A statement of the benefits to both the consumer and to the public expected from the proposed change.
2. Potential risk of harm to the consumer as a result of the proposed change, and factors to mitigate this risk.
3. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated.
4. Relevant comparative data for like compounds.
5. Local data or special considerations relating to New Zealand.
6. Interactions with other medicines.
7. Contraindications and precautions.
8. Possible resistance.
9. Adverse events - nature, frequency, etc.
10. Potential for abuse or misuse.

29/2/2016

Medicines Classification Committee (MCC)

Medsafe

Ministry of Health

Wellington

CC: College of general Practitioners

Re: The Reclassification of Selected Oral Contraceptives

Women's Health Action is a health promotion, information and consumer advisory service. We work with health professionals, policy makers and other not for profit organisations to influence and inform government policy and service delivery for women. We provide evidence-based analysis and advice to health providers, NGOs and DHBs, the Ministry of Health, and other public agencies on women's health (including screening), public health, and gender and consumer issues with a focus on reducing inequalities.

We have made a previous submission on the proposal to Reclassify Oral Contraceptives (Application to Reclassify Oral Contraceptives, January 2015 by Green Cross Health and Pharma Projects Ltd).

We are extremely disappointed to hear that the MCC has received a further application for reclassification which was not made publically available without seeking additional comment from key stakeholders. We support the comments made by the Royal NZ College of General Practitioners in their

Women's Health Action Trust
ph. 09 520 5295 | **e.** info@womens-health.org.nz | **w.** www.womens-health.org.nz | **f.** www.facebook.com/womenshealthaction

letter of 9th February 2016. We believe MCC must undertake a full, transparent and robust consultation on this issue and are seriously concerned about the MCC's processes so far.

In regard to the proposal, Women's Health Action (WHA) agrees that access to affordable and available contraception needs to be improved, especially for certain groups such as young women and rural women. However it is essential that this is done safely and that patient rights to informed consent, privacy and equitable health care are protected. This includes the right to be seen by a properly trained health professional.

In 2014, Green Cross Health Ltd first applied to reclassify oral contraceptives. At this point questions were raised about integrated care, collaboration, pharmacist training, and pharmacist management of the patient. **We do not think the subsequent 2015 application has addressed all these issues in sufficient detail and believe the application should be refused at this time and other options to provide safe, affordable and accessible contraception to women and men be investigated.**

We are concerned about the following issues:

1. **The proposal will not improve access:**

We agree with NZ Family Planning (NZFP) that compared with pharmacists, Family Planning nurses are trained and well placed to prescribe contraceptive pills. A rapid way to improve access to contraception would be to allow more primary care nurses to prescribe contraception. Promoting this role for nurse practitioners in PHOs, particularly in areas without a Family Planning Clinic (FPC), or providing mobile family planning services in some areas, would provide more affordable access and may be less daunting than a doctor's visit. There is also a need to provide culturally appropriate contraception and advice to some population groups.

2. **Addressing the cost of contraception**

The proposal does not indicate the costs that pharmacists would apply to this service and we believe the proposal contains no evidence that pharmacist supply will reduce costs for contraceptive users. Indeed

it is probable the pharmacy fee plus the cost of the medication when not prescribed by a doctor will increase the cost above that currently charged by NZFP.

3. Addressing health equity

The proposal may improve access for women living in areas with limited access to GPs and Family Planning clinics and potentially, youth. However, disparities are not necessarily addressed if the services provided are not of the same standard as provided by a GP, primary care nurse or Family Planning clinic. There is no evidence that the priority groups for greater contraceptive access including young people, Māori and Pacific women and women with low incomes will necessarily benefit. More research and investigation is required in this area and in ascertaining the effects on health disparities.

4. Ensuring professional behaviour

There are no elements in this proposal that address the possibility of unprofessional behaviour by pharmacists in the context of them being alone in private rooms with female patients. There have been media reports and we have received several anecdotal reports of pharmacists taking a judgmental or inappropriate approach to providing emergency contraception, including asking intrusive questions about sexual behaviour. We are also concerned about the ability of some pharmacies to provide a private interview area. We are concerned there is no way of monitoring such incidents and none of the checks and balances in place for nurses and doctors are in place for pharmacists. We have some concerns that busy pharmacists may fail to find the time to undertake adequate assessment.

5. Ensuring appropriate risk assessment

As NZFP have noted, family violence screening is now routinely practiced in Family Planning and most primary health care practices in New Zealand. Women who see pharmacists will miss out on this screening and intervention. We also think a limitation of pharmacist-supply of oral contraceptives is the missed opportunity for opportunistic screening for a range of other health issues such as STIs, cervical smears, smoking cessation advice, alcohol advice, and discussion about general well-being and for ongoing monitoring of any side effects.

Similarly, we believe that it is common for patients and health professionals to find it difficult to assess certain risks, for example if a patient's migraines are the type that contraindicate a combined oral contraceptive. We do not agree that women will necessarily recognise their contraindications or know the range of risk factors that should be assessed.

6. **Breastfeeding**

There is clear evidence that some forms of contraception should not be used while breastfeeding. We are concerned that a pharmacist may not be aware a woman is breastfeeding or may encourage stopping breastfeeding early to start on oral contraception. We are also concerned that pharmacists have an interest in promoting the use of infant formulas.

7. **Vested interests**

Pharmacists have a financial interest in selling these products and cannot be said to be immune to these and other commercial pressures.

If the proposal should be accepted attention must be paid to the following issues:

1. **Training programmes**

An approved, evaluated training programme followed by regular update sessions must be put in place. The programme must cover ethical issues, risk assessment and informed consent, assessment of high-risk women to ensure they do not receive oral contraception when they are at high risk of complications, teaching of pill-taking so that women use the packets correctly and know what to do if they forget pills, and information about STIs, use of condoms, cervical screening etc.

Pharmacists should be required to display evidence they have undertaken the programme.

2. **Age limit**

While we agree that young women have a right to contraception we believe this should be provided in the context of a full health assessment including monitoring of other issues such as family violence,

coercion or STIs. Pharmacists should not be providing contraception to anyone under 16 or first time contraception to anyone under 18.

3. **Staged approach**

There should be a staged approach, which includes auditing by a doctor.

4. COC and POPs

Only the less risky POPs should be prescribed.

5. Privacy

Pharmacies must have a fit for purpose designated private room (i.e. not a store room or tea room), which is provided for interview for any form of contraception including emergency contraceptives.

6. Informed consent

The information materials we have reviewed are not entirely objective, are too long and set at a high literacy level. A robust information and informed consent process must be developed that is set at a lower literacy level, is accessible and clear. Information must also be provided verbally, in a language the patient can understand.

7. Collaborative agreements

We support the use of Collaborative Practice Agreements. The submission for the proposal mentions that many international pharmacist-supply programmes for oral contraception involve collaborative practice agreements where the pharmacist works with a doctor. We also agree initial audit by a doctor, should be an essential part of any training programme.

In conclusion, Women's Health Action agrees that access to contraception must be improved, especially for certain groups such as young women. However, we do not think that this proposal is a safe or effective way of doing so.

We believe that contraception should be provided in the context of overall health care, assessment of risk factors and ongoing monitoring. While seeming to offer an advance in healthcare for women, this proposal in fact is likely to result in more costly and less effective health care and to increase risk. As such we share the RNZCGP's concerns.

While it is not in the domain of the MCC to make such decisions, we would prefer to see increased family planning and PHO resources put in place and that contraception be provided free of charge to New Zealand women.

Best regards,

Dr Sandra Hall

for Women's Health Action Trust

email: sandy@womenshealth.org.nz

Johnson & Johnson Pacific

Monday, 14th March 2016

Medicines Classification Committee
Medsafe
PO Box 5013
Wellington 6145

Dear Sir/Madam,

Re: Item 5.2.3 Review of tramadol and codeine reclassification

Johnson & Johnson (New Zealand) Limited (JJP) appreciates the opportunity to provide comment on agenda item 5.2.3 review of tramadol and codeine reclassification, to be discussed at the 55th meeting of the medicines classification committee.

JJP is the sponsor of medicines that contain codeine, in combination with paracetamol and phenylephrine (PE). These products are indicated for the relief of symptoms associated with colds and flu under the brand name of Codral, a local brand that can only be found in Australia and New Zealand. JJP does not market single active or combination analgesics in either Australia or New Zealand.

A summary of codeine use in New Zealand was presented to Sarah Reader and Andrea Kerridge in June 2015. For the benefit of the committee, a copy of the presentation is provided in **Attachment 1**. The slide deck has not been updated to include the consolidated sales figures for 2015. Consistent with the situation in Australia, restricting the access to codeine containing analgesics has not resulted in category cross-over with products that contain codeine (i.e. the is no transfer of users from codeine containing analgesics to codeine containing cold and flu products). Further there is no evidence of codeine abuse with codeine containing cold and flu products within New Zealand.

Of particular interest is that the re-classification of codeine containing analgesics has been more successful in New Zealand when compared with Australia. This observation has been shared with the TGA in a recent meeting with key members of the TGA with an interest in this area. A copy of the presentation made to the TGA is provided in **Attachment 2**. None of the ACMS members were present at the meeting.

The scheduling delegate proposed the following:

Scheduling Proposals for Codeine

Schedule 2 (cough and cold medicine preparations):

a. Proposal to amend the Schedule 2 entry to reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction; OR
b. Proposal to up-schedule the Schedule 2 entry to Schedule 3 and reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction; OR
c. Retain the interim decision to up-schedule to Schedule 4.

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

a. Proposal to amend the Schedule 3 entry to reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction; OR
b. Retain the interim decision to up-schedule to Schedule 4.

In response to this proposal JJP made a submission to the ACMS. A full copy of this submission is provided in **Attachment 3**. In brief, JJP presented the following:

- JJP maintain the position that the evidence shows that there is no abuse or misuse of codeine containing cold and flu products and will continue to actively monitor the situation.
- JJP supports the proposal for maintaining the S2 scheduling of codeine containing cold and flu products when supplied with new label warnings as proposed. Whilst questioning the impact, JJP does not oppose limiting the pack size to no more than 3 days supply.
- JJP strongly opposes other scheduling proposals for codeine containing cold and flu products.
- JJP supports the proposal to maintain the S3 scheduling of codeine containing analgesics limited to 3 days' supply with the additional label warnings as proposed.
- JJP's support of the S3 scheduling proposal for codeine containing analgesics is contingent on the introduction of a real time monitoring systems that has been proposed by ASMI
- JJP recommends that a well-designed, scientifically robust, Australia wide study on mortality rates associated with codeine misuse/abuse in OTC products, pre and post all codeine related scheduling decisions and other implemented measures (such as a real time monitoring system) be undertaken to determine the success of these measures in a systematic and accurate manner.

The concerns that JJP had with the scheduling proposals from mid 2015 (to make all codeine containing products S4) included but were not limited to:

1. There was no differentiation between codeine containing analgesics and codeine containing cold and flu products.
2. The published evidence considered by the ACMS, in support of the misuse issue in Australia, was based on data collated prior to the initial up-scheduling of the codeine containing analgesics and was therefore years out of date and not representative of the current situation.
3. There has been no comprehensive national review on morbidity and mortality associated with codeine considering both pre- and post- the up-scheduling of codeine containing analgesics.
4. Evidence of abuse has never been published in the public domain and individuals or companies have not been afforded the opportunity to review and analyse the evidence.
5. Not all regulatory options had been explored by the TGA. Whilst Medsafe had proactively requested sponsors to include addiction warnings on codeine containing products. These warning statements had not been made mandatory by the TGA.

JJP would like to thank the MCC for this opportunity to provide comment on the scheduling proposals for Codeine in Australia. If the committee sees benefit in doing so, I would be more than happy to make myself available to present any or all of the data the JJP has in relation to codeine use in Australia and New Zealand. Please feel free to contact me should you need provide further data or information.

[redacted]

Johnson & Johnson Pacific

Attachment 1
JJP Presentation to Sarah reader and Andrea Kerridge
June 2015

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45 JONES STREET, ULTIMO NSW 2007, AUSTRALIA. TELEPHONE: 131 565, FACSIMILE: (02) 8260 8109
ADDRESS ALL COMMUNICATIONS TO: LOCKED BAG 5, BROADWAY, NSW 2007


Johnson & Johnson Pacific

Influence of Scheduling Change on OTC Codeine Containing Analgesics and the Potential Relationship with Codeine Containing Cough & Cold Products in New Zealand
2009 to 2014

[redacted]

Johnson & Johnson Pacific

Background to the OTC Codeine Analgesic Issue (and Cough and Cold Products containing codeine)

- Reports of individuals consuming excessive doses of ibuprofen codeine combinations leading to severe adverse events motivated the NDPSC to up-schedule all OTC codeine containing analgesics to Pharmacist Medicine, implemented in 2010.

- New pack size restrictions to four days supply (max pack size of 40 tablets – previously 72) and label warnings

- Although cough & cold medicines containing codeine were not implicated and scheduling remained unchanged as Pharmacy Medicine, days supply, pack size and labelling changes were imposed

- Some reporting of chemical diversion of codeine from analgesics

Would tighter restrictions to OTC analgesics with codeine affect demand for cough cold products?

- NDPSC expressed concern about the potential for an increase in demand for cough cold products containing codeine ‘because they could be more easily accessed compared to the OTC analgesics’.

- Call to monitor supply of cough cold products with codeine to demonstrate no crossover in demand – data has been presented to demonstrate this (2011)

Reports of misuse of OTC codeine analgesics have continued in Australia

- Since schedule change to Pharmacist Only Medicine in 2010, intermittent reports about misuse of OTC codeine containing analgesics and mostly GI morbidity AEs have continued in Australia
- ACMS has placed OTC codeine on the July (August) agenda for review
- All products – Analgesics and Cough Cold – are to be considered
- J&J Pacific are sponsors of cough cold products containing codeine, but not analgesics containing codeine

Aim

- To present annualised data on the impact of scheduling and pack size changes to the analgesics with codeine and cough cold with codeine product categories, covering the timeframe through which the scheduling change occurred; 2009 to 2014.

- To demonstrate and confirm the lack of association between demand for cough cold products with codeine, and OTC analgesics with codeine

Data sources and description

- Full 12 month annual data over the 6 years 2009 to 2014, covering the period of schedule change – all brands.

- Pharmacy data from IMS measuring supply, representing >90% of volume

- Grocery data from AZTEC point of sale from 2010 – statistical representation – cough & cold only. - - > No grocery data for analgesics.

- Data collected as total number of tablets/24 thus like for like analysis. Paediatric, herbal and liquids excluded.

Data sources and description

- Paracetamol (Par), Ibuprofen (Ibu), with and without codeine (w C; w/o C) and multi-combination with codeine (Tens) data.

- Single ingredient analgesics of 100 or more tablets excluded (non-”OTC”/prescription/pharmac).

- Cough and Cold with Codeine (C&C w C) and without (C&C w/o Cod) in pharmacy, and C&C in grocery, represented.

- De-identified – no brand names

Outcomes Summary

- There has been a substantial fall in supply of packs of OTC analgesics with codeine as a result of the schedule changes in 2010

- Single ingredient analgesics have overtaken analgesics with codeine, indicating the analgesic/codeine schedule change policy has proved successful.

- There has been a decline in supply of cough & cold without codeine in pharmacy that corresponds to the growth of this category in the grocery sector

Outcomes Summary

- Change to Pseudoephedrine scheduling as also impacted the cough cold sector

- There appears to be no relationship between the decline in supply of OTC analgesics with codeine, and cough & cold products with codeine. These two categories appear independent of each other

OTC Analgesics - NZ

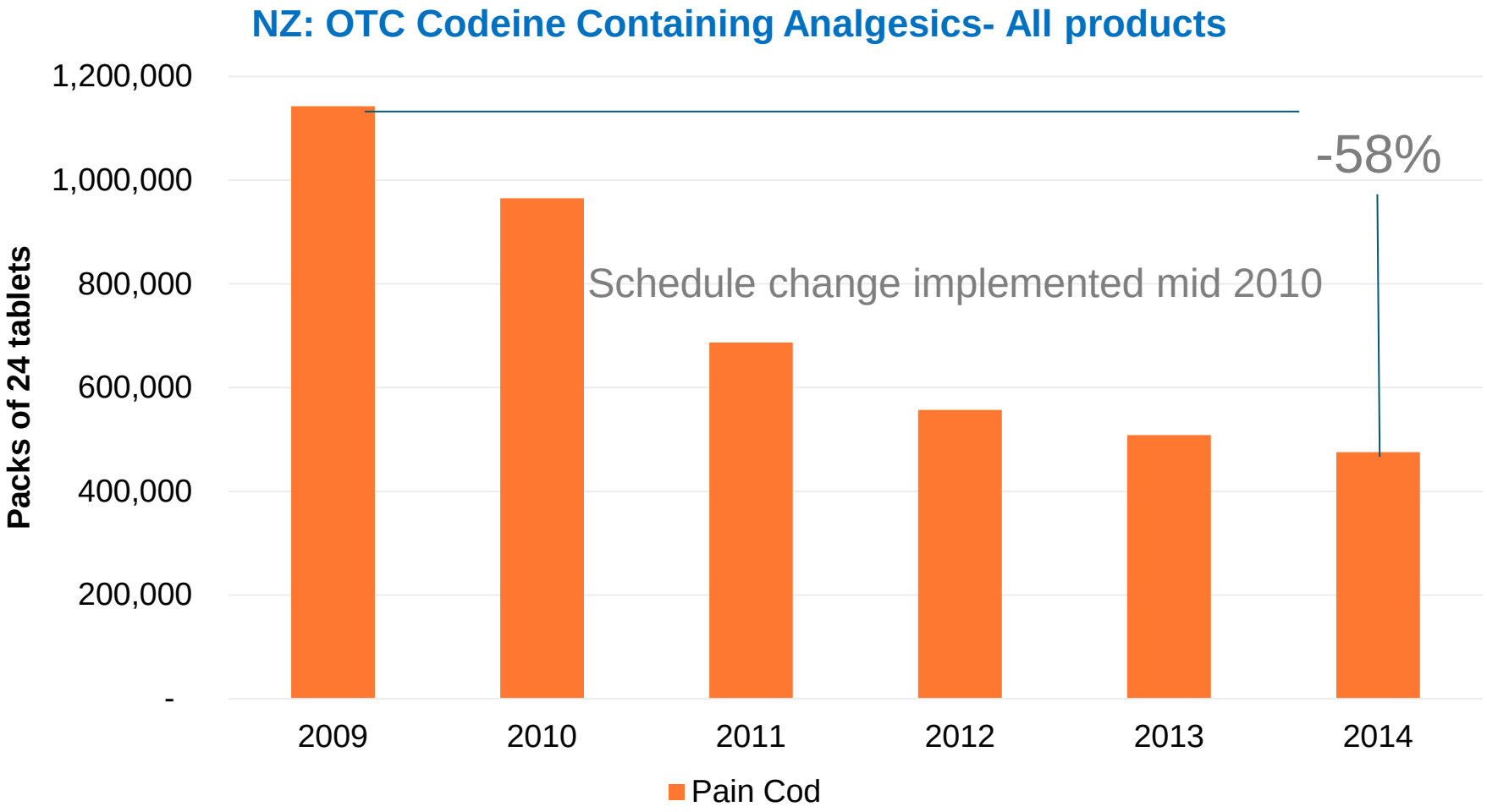
Pharmacy data IMS MAT 2009 to 2014

Packs of 100 tablets plus, excluded

All packs as 24 tablets

Johnson & Johnson Pacific

Up-scheduling and pack size change has clearly impacted the supply of OTC codeine containing analgesics in NZ



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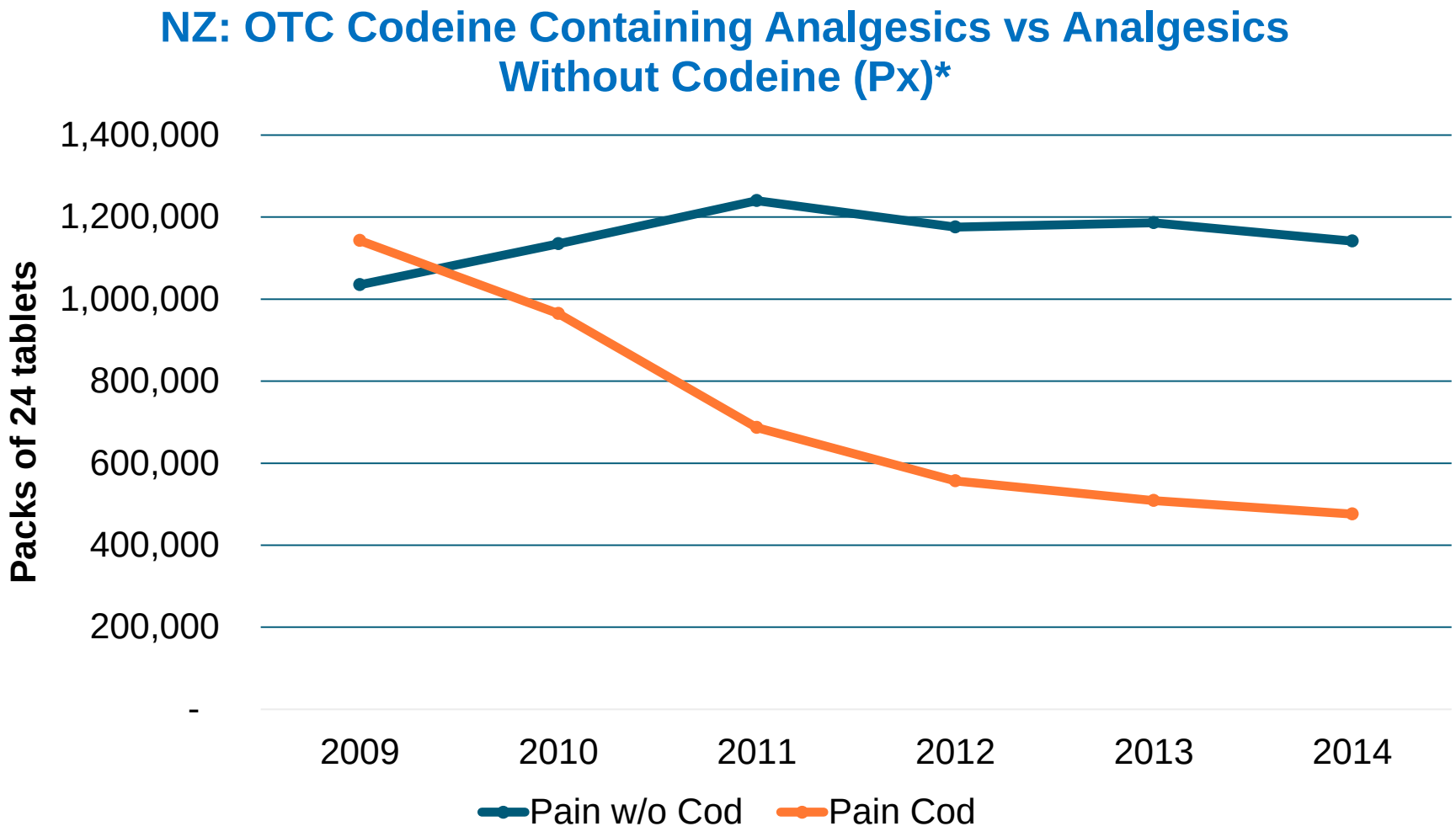
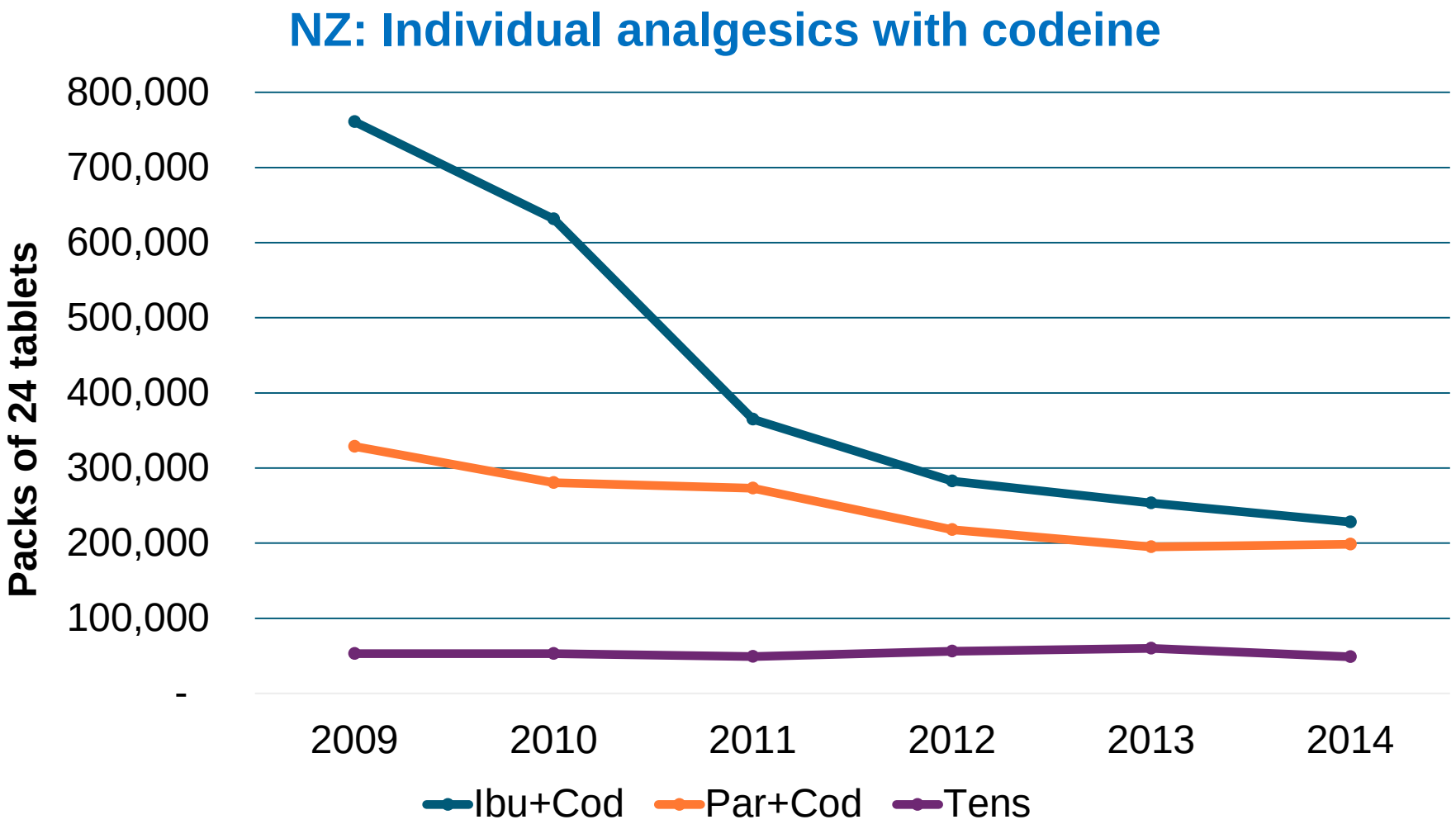
Growth in analgesics without codeine over those with codeine indicates scheduling policy is effective



*Limited to analgesics without codeine supplied through pharmacy. Grocery analgesic data not available

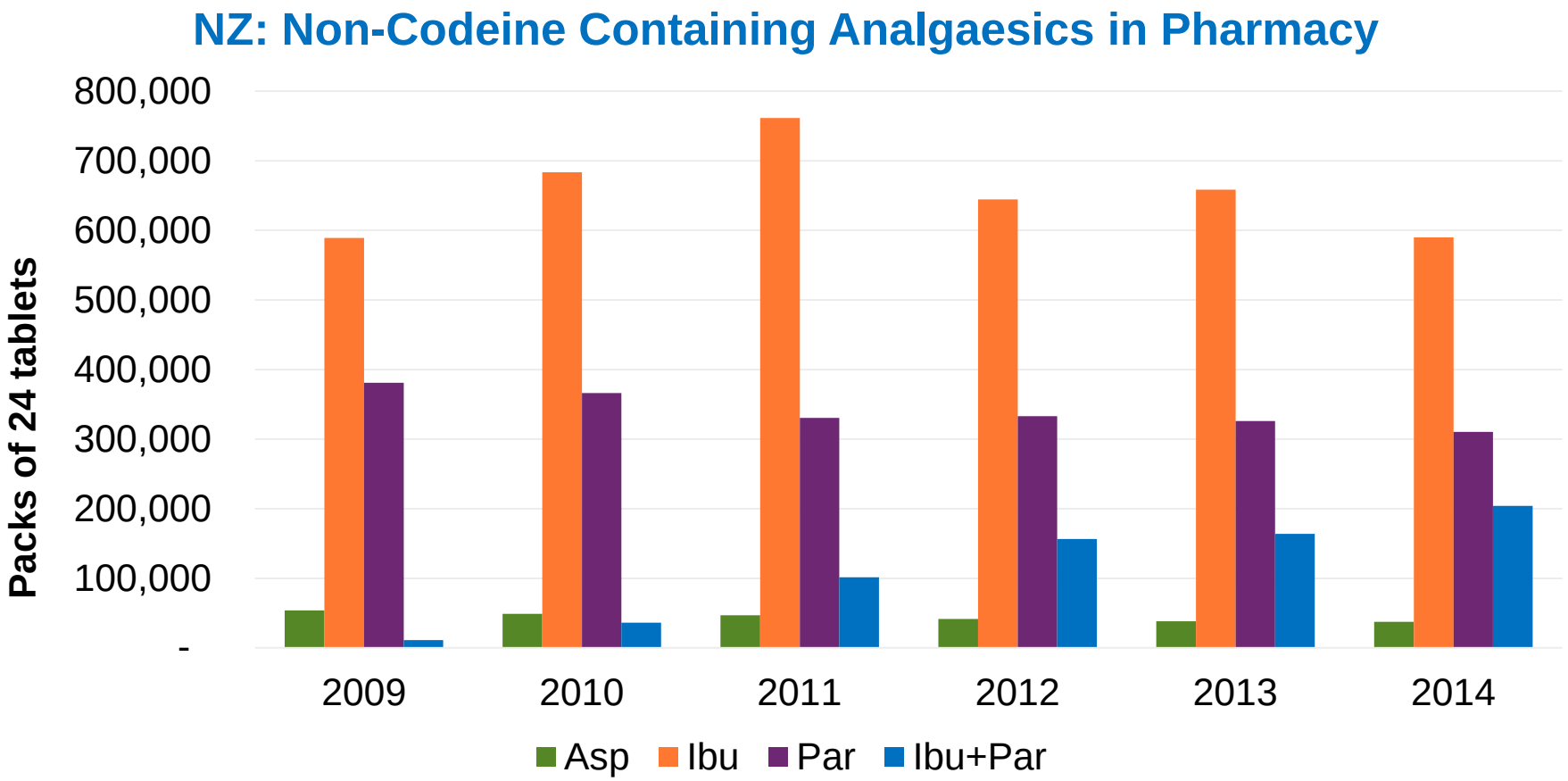
Johnson & Johnson Pacific

Ibuprofen codeine combination products are those with the most significant decline since 2009



Johnson & Johnson Pacific

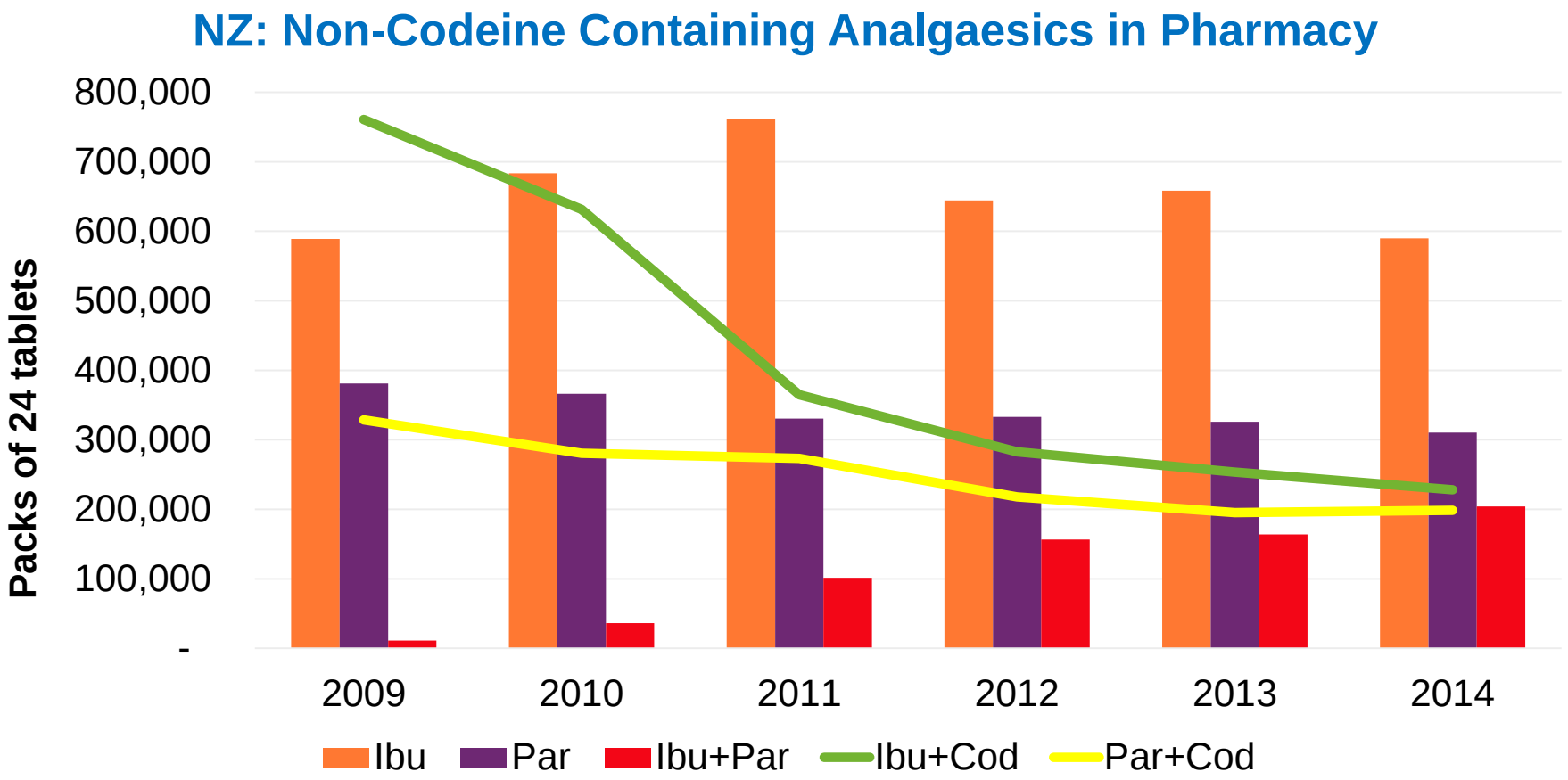
Paracetamol and ibuprofen monotherapies appear affected by growth of their combinations and those with caffeine (Ibu+Par)* and probably grocery analgesic supply.



*Ibu+Par also includes Par plus caffeine

Johnson & Johnson Pacific

Appears ibuprofen single ingredient initially replaced its codeine combination to 2011, followed by Paracetamol/ibuprofen and caffeine combinations



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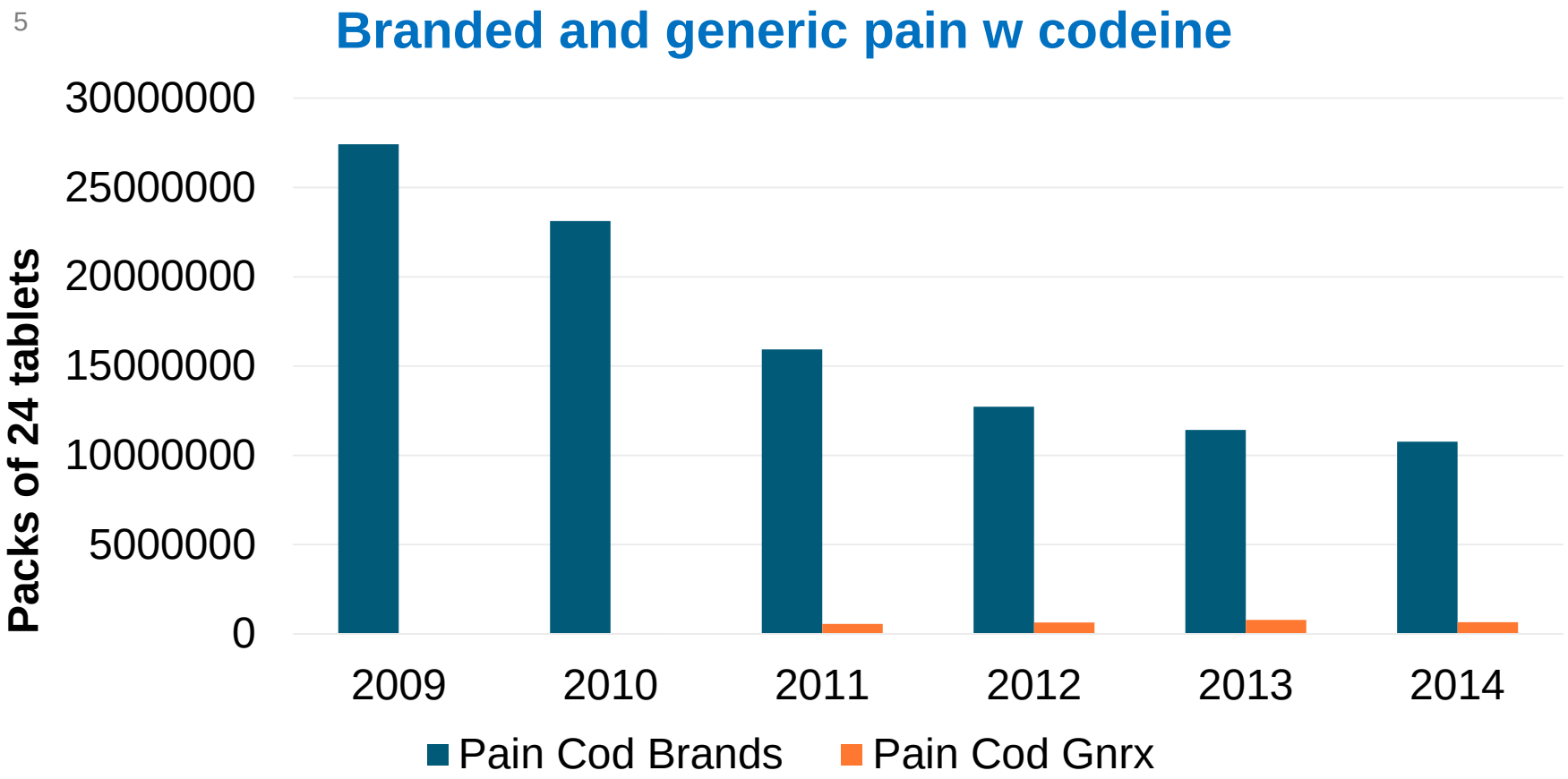
Although minor sponsors in NZ, generic/private label products should comply with voluntary label changes to OTC codeine analgesics proposed by industry



OTC Cough & Cold - NZ

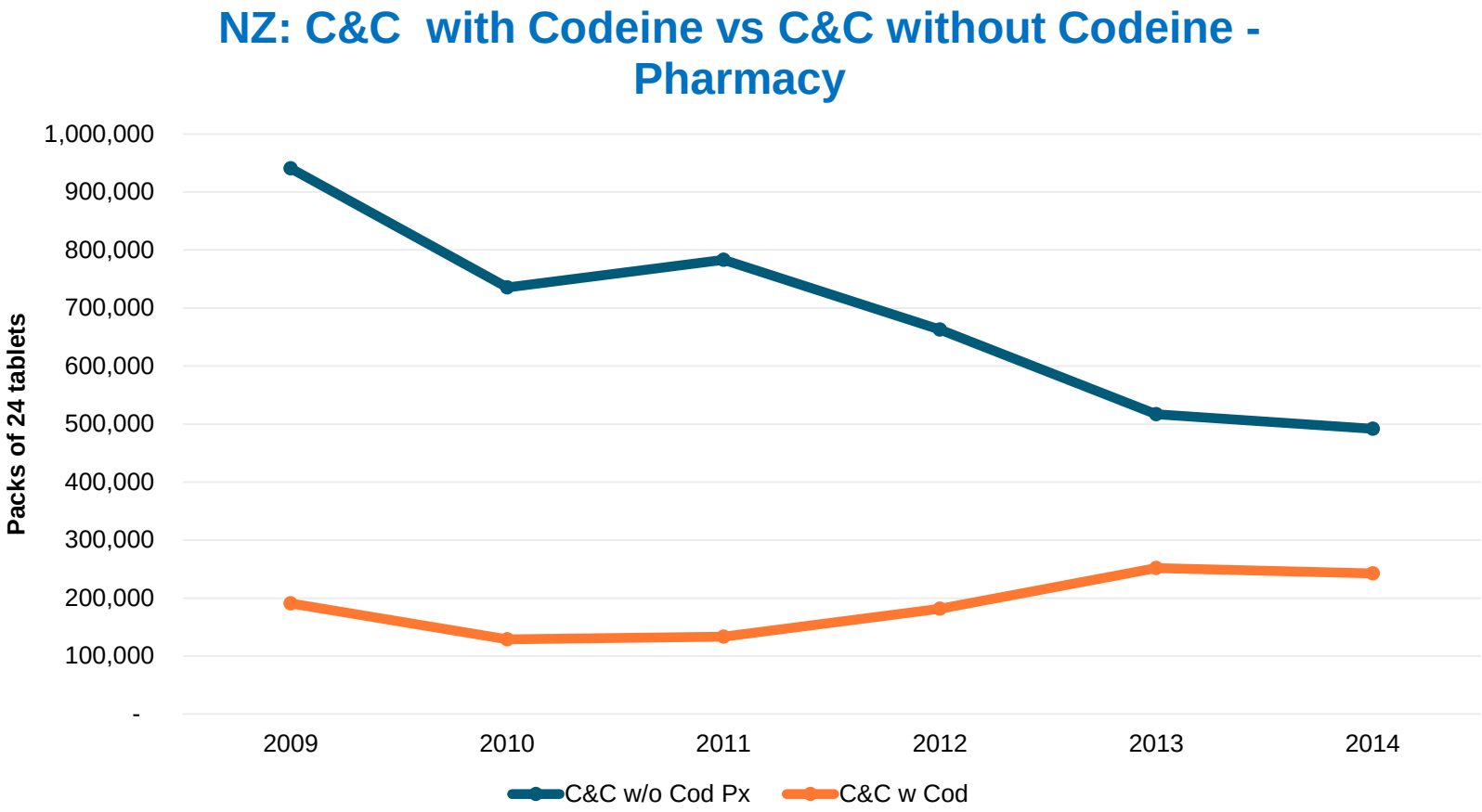
Pharmacy data IMS MAT 2009 to 2014

Grocery data AZTEC MAT 2010 to 2014

All packs as 24 tablets

Johnson & Johnson Pacific

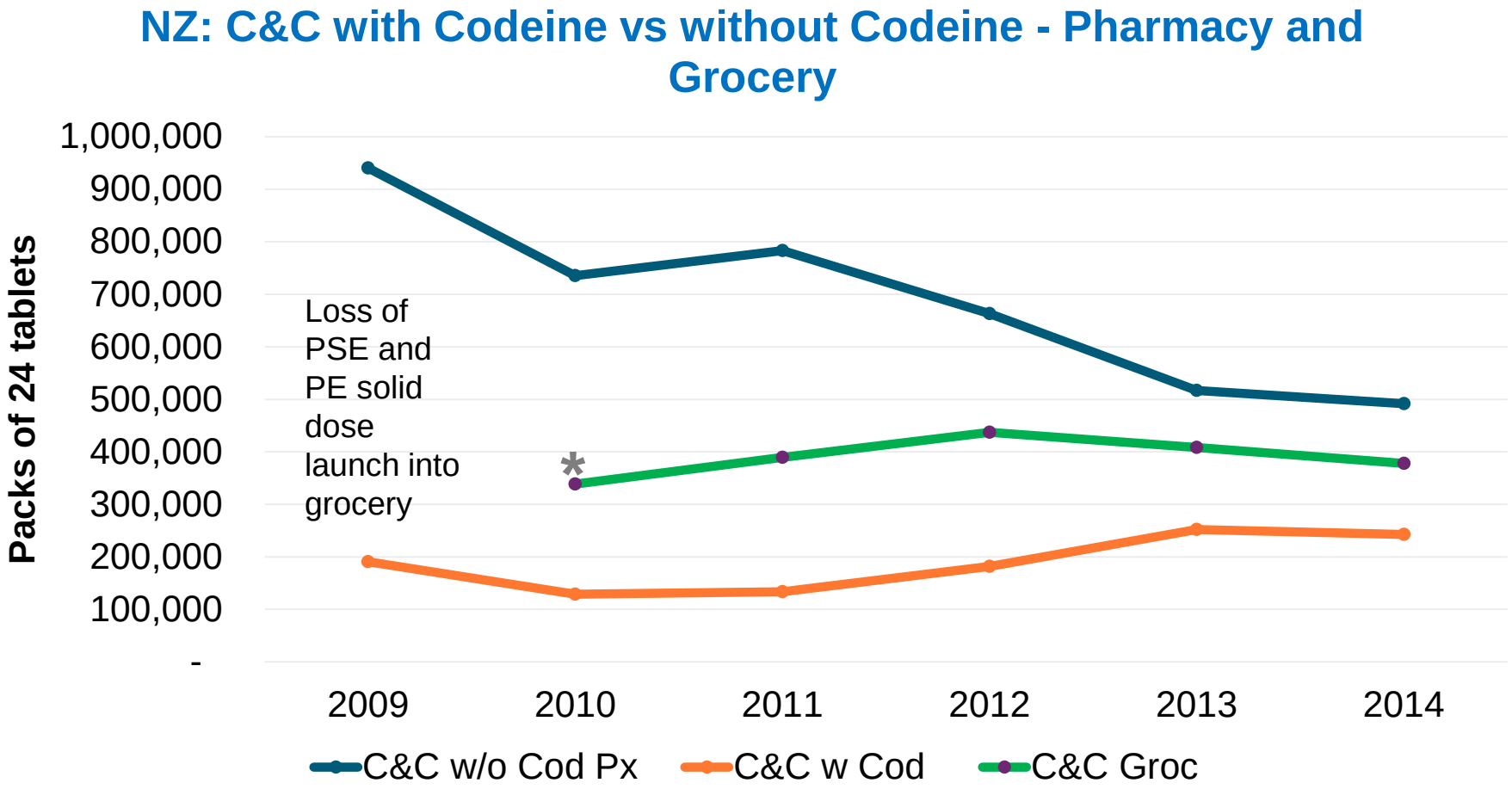
Although there has been a consistent fall in supply of C&C products without codeine* since 2009, there is not a corresponding spike in demand for products with codeine



*Most cough cold products without codeine contain PE. All with codeine contain PE

Johnson & Johnson Pacific

Fall in supply of products without codeine in pharmacy corresponds with grocery PE product launch and schedule change of pseudoephedrine



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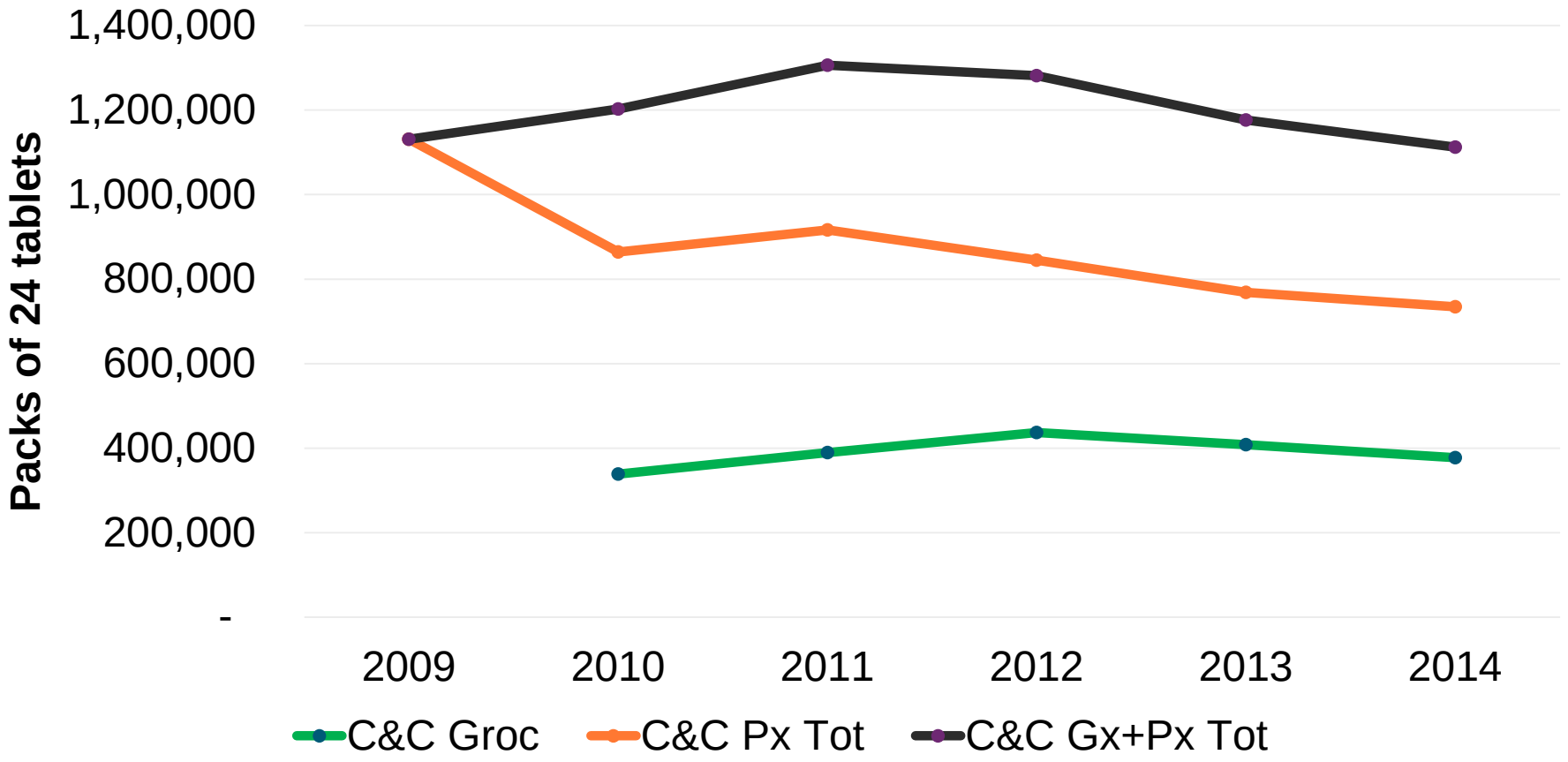
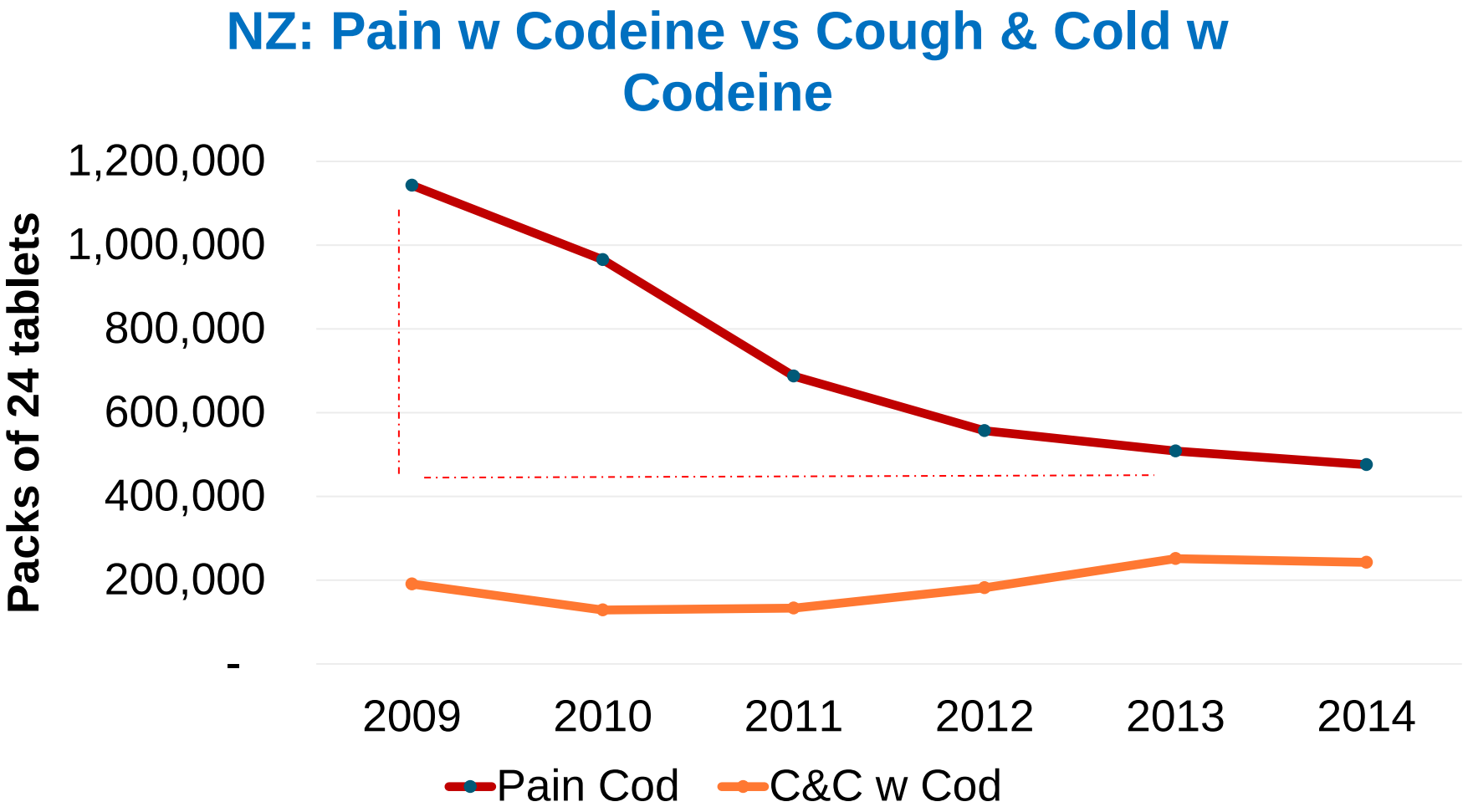
* Grocery data only available from 2010

Pharmacy C&C has been impacted by grocery with overall trend pointing to a modest decline since 2011. Unlikely pain codeine has had much influence.

Impact of Grocery on C&C product distribution in NZ



The size of the fall of pain with codeine is not reflected by an increase in demand for C&C with codeine.



Johnson & Johnson Pacific

Influence of Scheduling Change on OTC Codeine Containing Analgesics and the Potential Relationship with Codeine Containing Cough & Cold Products in NZ 2009 to 2014

Conclusions

- There has been a substantial fall in supply of packs of OTC analgesics with codeine as a result of the schedule changes implemented in 2010
- Single ingredient analgesics have overtaken OTC analgesics with codeine, indicating the analgesic/codeine schedule change policy has proved successful.
- There has been a decline in supply of cough & cold without codeine in pharmacy that corresponds to the growth of this category in the grocery sector

Johnson & Johnson Pacific

Influence of Scheduling Change on OTC Codeine Containing Analgesics and the Potential Relationship with Codeine Containing Cough & Cold Products in NZ 2009 to 2014

Conclusions

- Change to Pseudoephedrine scheduling as also impacted the cough cold sector
- There appears to be no relationship between the decline in supply of OTC analgesics with codeine, and supply of cough & cold products with codeine. These two categories appear independent of each other
- Scheduling and pack sizes of Cough & Cold product with Codeine remains appropriate

Johnson & Johnson Pacific

Attachment 2
JJP Presentation to the TGA
March 2016

JOHNSON & JOHNSON PACIFIC PTY LIMITED ABN. 73 001 121 446
45 JONES STREET, ULTIMO NSW 2007, AUSTRALIA. TELEPHONE: 131 565, FACSIMILE: (02) 8260 8109
ADDRESS ALL COMMUNICATIONS TO: LOCKED BAG 5, BROADWAY, NSW 2007

Influence of Regulatory Changes on the Supply of OTC Cold Treatments *(2007 to 2015)* & OTC Analgesics *(2009 to 2015)* in Australia

March 2016

[redacted]

[redacted]

Johnson & Johnson Pacific

Agenda

- Cold & Flu Treatments with & without Codeine
- Analgesics with & without codeine (Pharmacy Trends)
- Category Cross-over?
- Pseudoephedrine – A Case Study for Codeine Analgesics
- Pack Size Restrictions for Codeine Products
- Observations and Conclusions

[redacted]

Data Source & Timing

imshealth™

Provides data on pharmaceuticals supplied to all pharmacies across Australia

IRi | Aztec

Provides data on all products sold (scanned) by all major grocery outlets

- J&J holds historic IMS and AZTEC data for the Cold Treatment market, from 2007 to 2015.
- Data for the Pain Treatment sector is only available from 2009 to 2015 and is limited to Pharmacy Only.
- J&J is not active in the analgesic sector in AU.
  - J&J does not purchase data for marketing planning purposes
  - J&J has invested specifically to obtain analgesic data for regulatory purposes

Like-for-Like Analysis

- The analysis has been limited to solid dose formats
- Every ‘pack’ has been calculated as a pack of 24 ‘tablets’.
  - i.e. all pack sizes have been calculated as the number of tablets per individual pack X the volume of packs supplied, divided by 24.
- Removes complexity of myriad of pack sizes
- All brands across all Sponsors are represented and not limited to J&J.

Exclusions

- Packs of 100 tablets or more have been excluded from the analysis (all single ingredient analgesics)

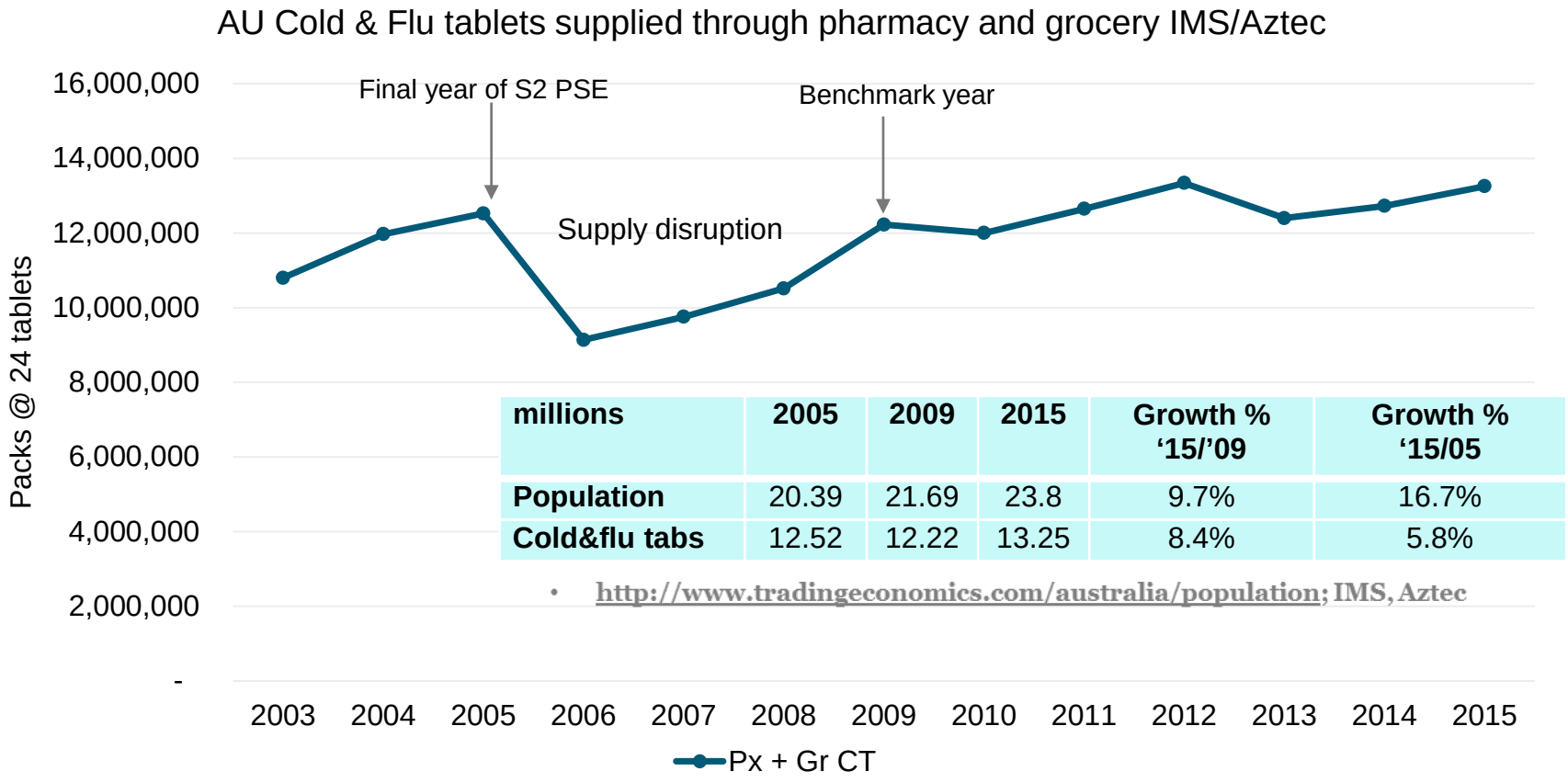
Cold & Flu Products
with & without Codeine
Trends in Pharmacy and Grocery
2007 to 2015
IMS, AZTEC

[redacted]

Johnson & Johnson Pacific

Cold & flu treatment tablets supplied through pharmacy and grocery (Px+Gr CT) is below population growth between 2009 and 2015, and substantially below population growth between 2005 and 2015.

2009 is the analysis benchmark year due to supply disruption between 2005 and 2009. Supply resumed as normal from 2009

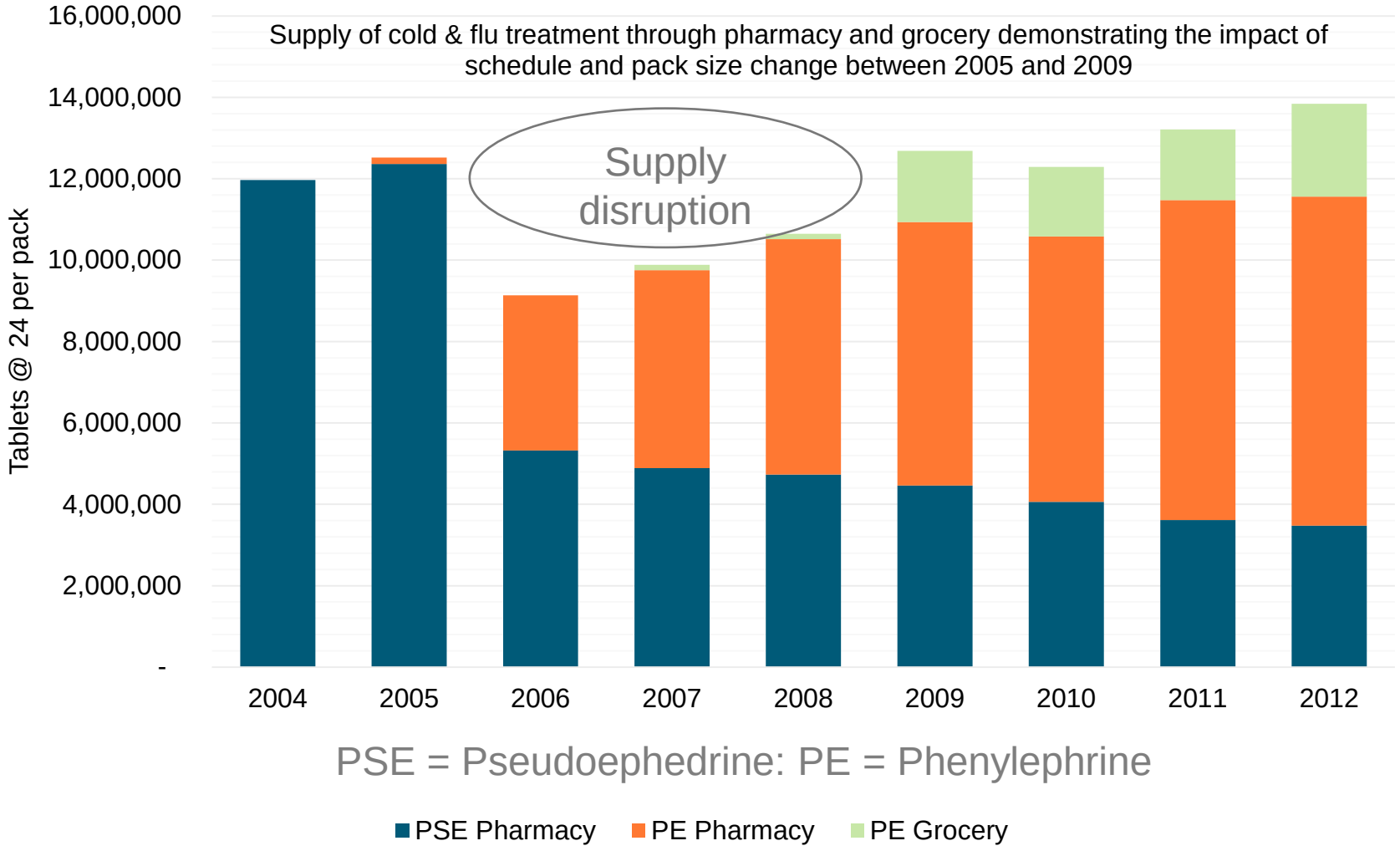


millions	2005	2009	2015	Growth % '15/'09	Growth % '15/05
Population	20.39	21.69	23.8	9.7%	16.7%
Cold&flu tabs	12.52	12.22	13.25	8.4%	5.8%

- http://www.tradingeconomics.com/australia/population; IMS, Aztec

Supply disruption – Resulted from companies not having PE formulations available it time of up-scheduling PSE

Disruption in supply after 2005 due to PSE rescheduling and slow response by Industry to produce PE alternatives. Supply returning to normal (benchmark) levels by 2009



Johnson & Johnson Pacific

Reason for supply disruption of cold & flu tablets between 2005 and 2009 is due to pseudoephedrine (PSE) re-scheduling and pack size limitation

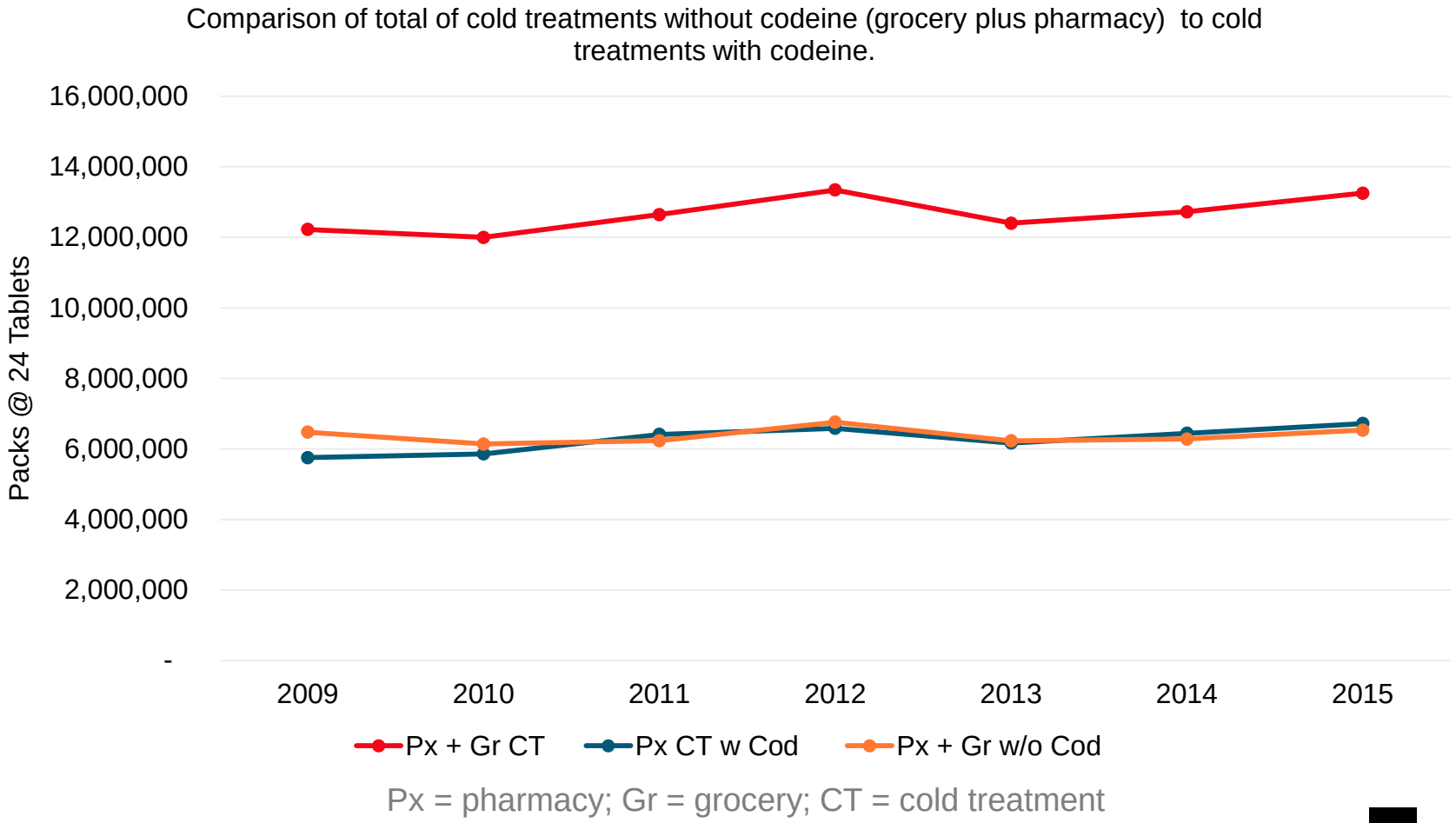
Pseudoephedrine (PSE) underwent a substantial regulatory change in 2006

- Multi Ingredient combinations became S3 (recordable) with a limit of 720mg PSE per tablet pack – causing substantial supply issues
- Industry was not ready for this change
- Prior to late in 2005, phenylephrine (PE) in tablet form was not available on the Australian market as a potential alternative to PSE
- Until 2009, there was only one major supplier of PE multi-combination cold and flu tablets, with limited capacity to supply the whole AU market

Supply resumed to "normal" levels from 2009

Overall cold & flu product growth (Px+Gr CT) is modest and below population growth (as described previously).

Supply of cold treatments with codeine (Px CT w Cod) and without codeine (Px+Gr w/o Cod) are similar and follow the same trend .

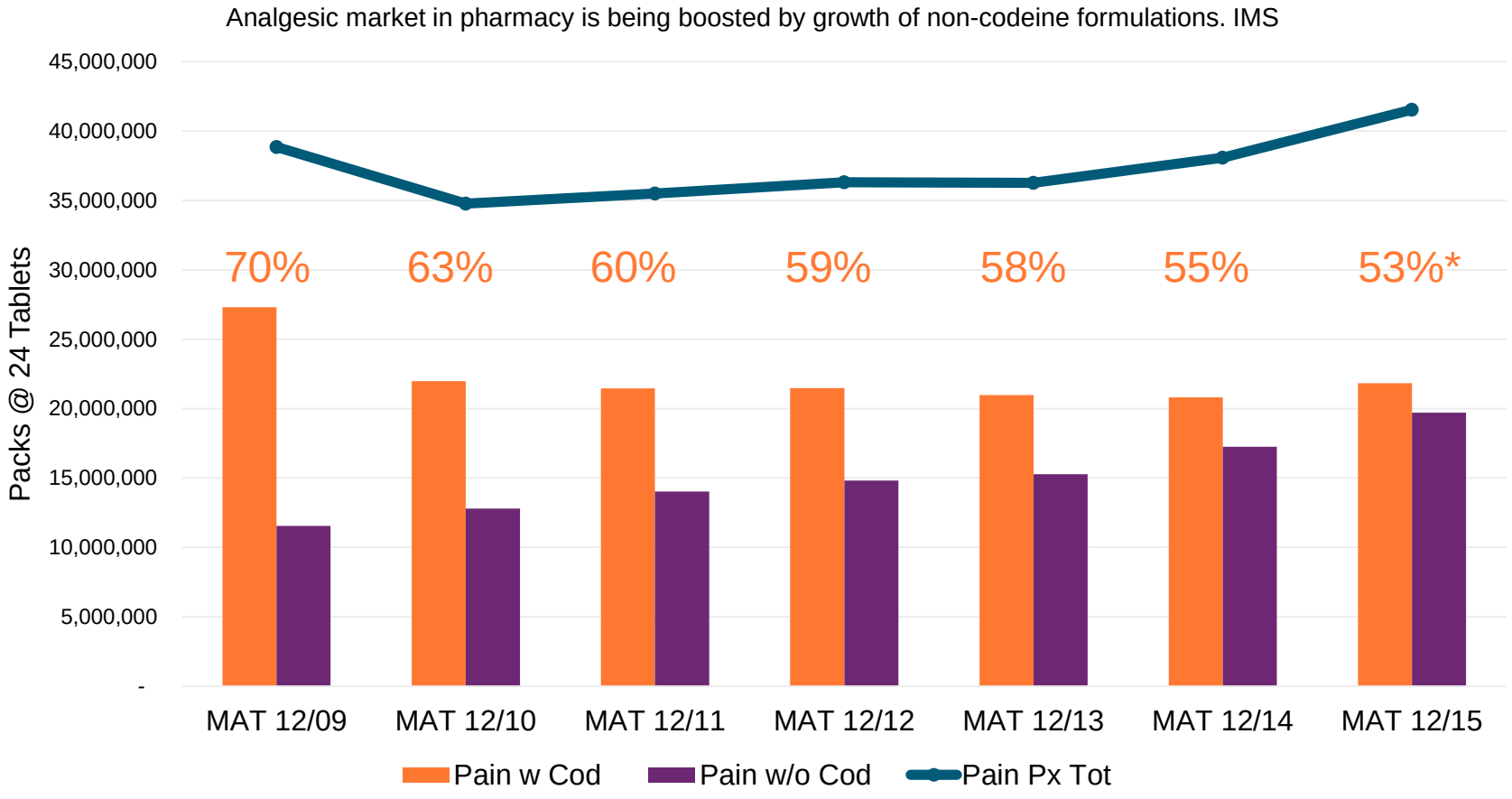


Px = pharmacy; Gr = grocery; CT = cold treatment

Analgesics With and Without Codeine
Trends in pharmacy
2009 – 2015
IMS

Johnson & Johnson Pacific

Schedule and pack size change led to the fall in supply of pain with codeine by ~ 5 million packs per year vs 2009. The strongest fall in supply is between 2009 and 2010. Market growth is due to non-codeine formulations



* Proportion of with to without codeine

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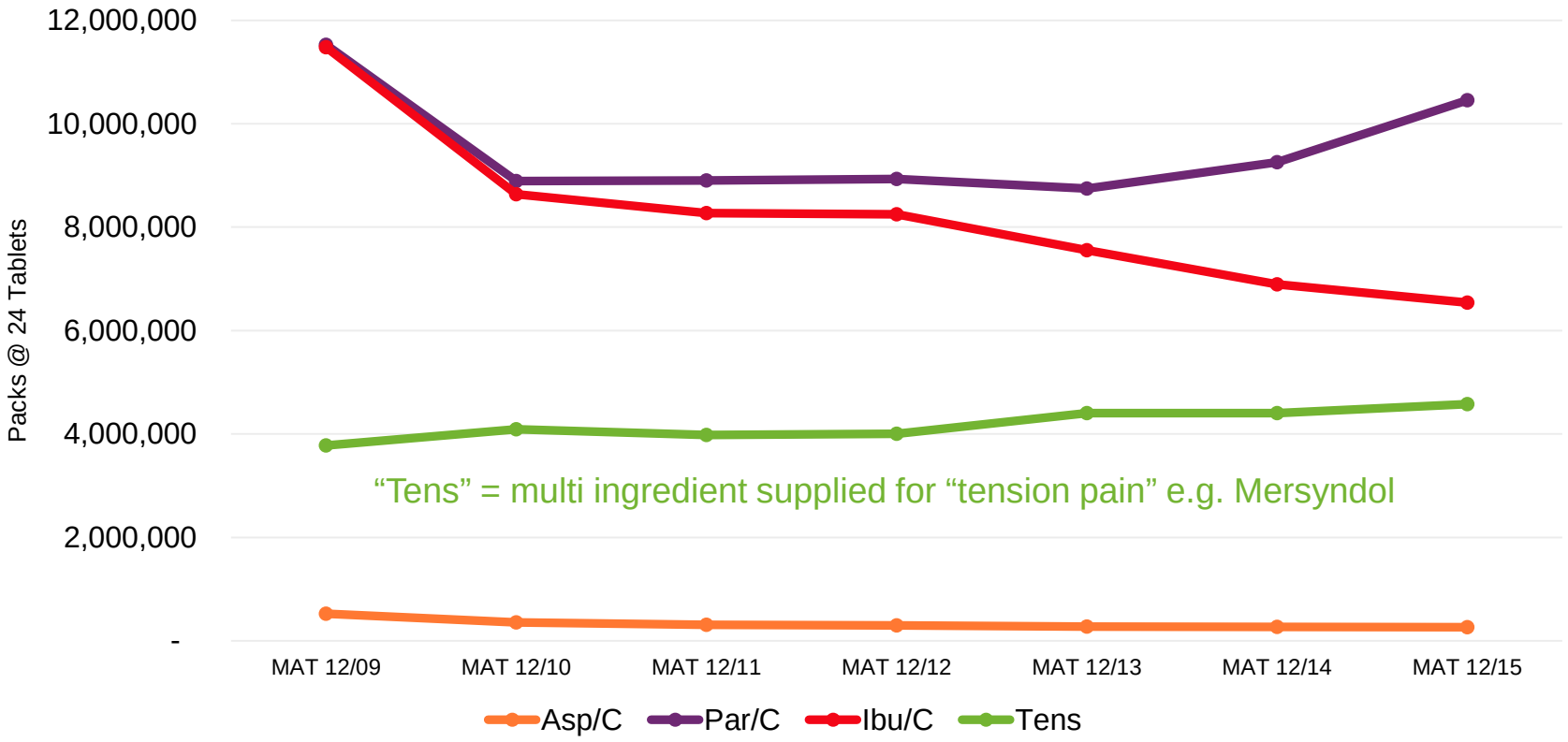
Fall in supply of pain treatments with codeine between 2009 and 2010 was similar across all states except for NSW. NSW was the only state allowing a pack size of >48 tablets as S2

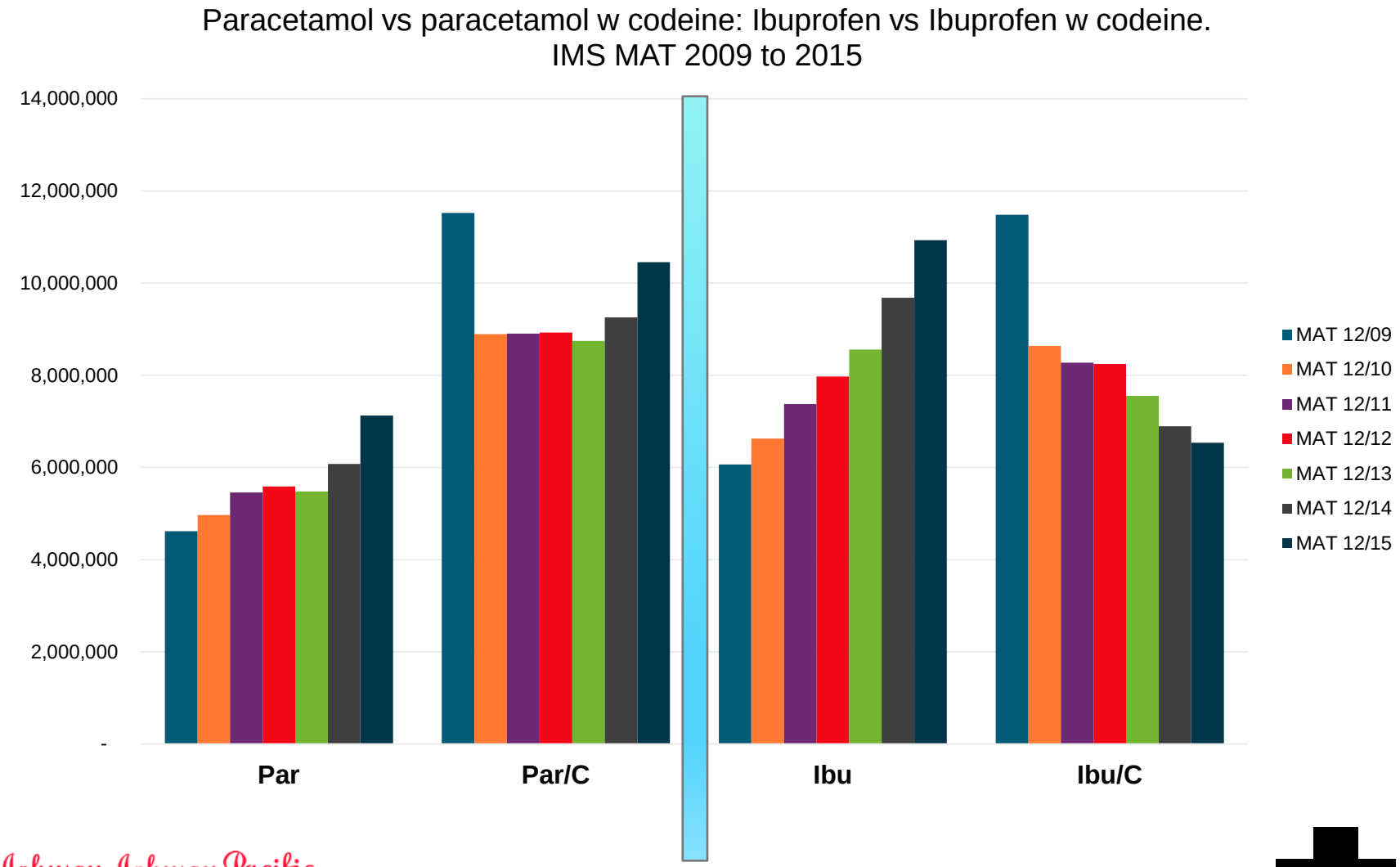
State	Fall in supply of OTC Pain Treatments Containing Codeine between 2009 and 2010
National Average	-20%
NSW	-26%
Victoria	-15%
Queensland	-16%
South Australia	-15%
Western Australia	-10%
Tasmania	-18%
Northern Territory	-20%

The regulatory changes in 2010 caused the fall in supply of ibuprofen and paracetamol with codeine, with no change to ‘tension’ or aspirin with codeine

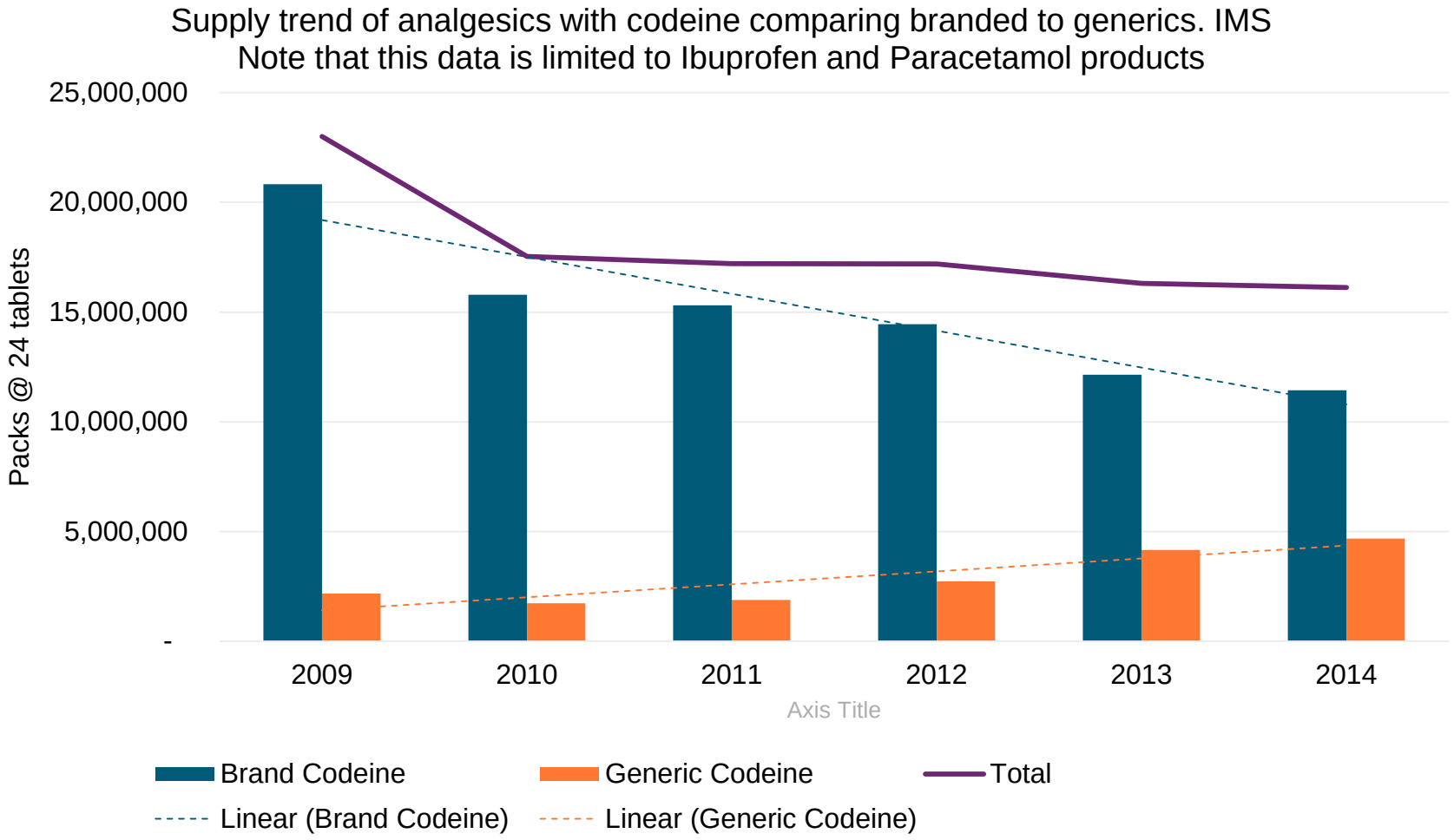
Codeine containing analgesics in pharmacy – trend over 7 years – demonstrating influence of schedule and pack size change in 2010. IMS.



Growth of paracetamol appears independent of paracetamol with codeine. Growth of ibuprofen appears as a consequence of the fall in in supply of ibuprofen with codeine



Fall in supply of pain with codeine is from branded products. Generics / private label are gaining share and growth at the expense of brands.



Association Between Fall in Supply of Analgesics With Codeine & Potential for Cross-Over Demand for Codeine Containing Cold & Flu Products?

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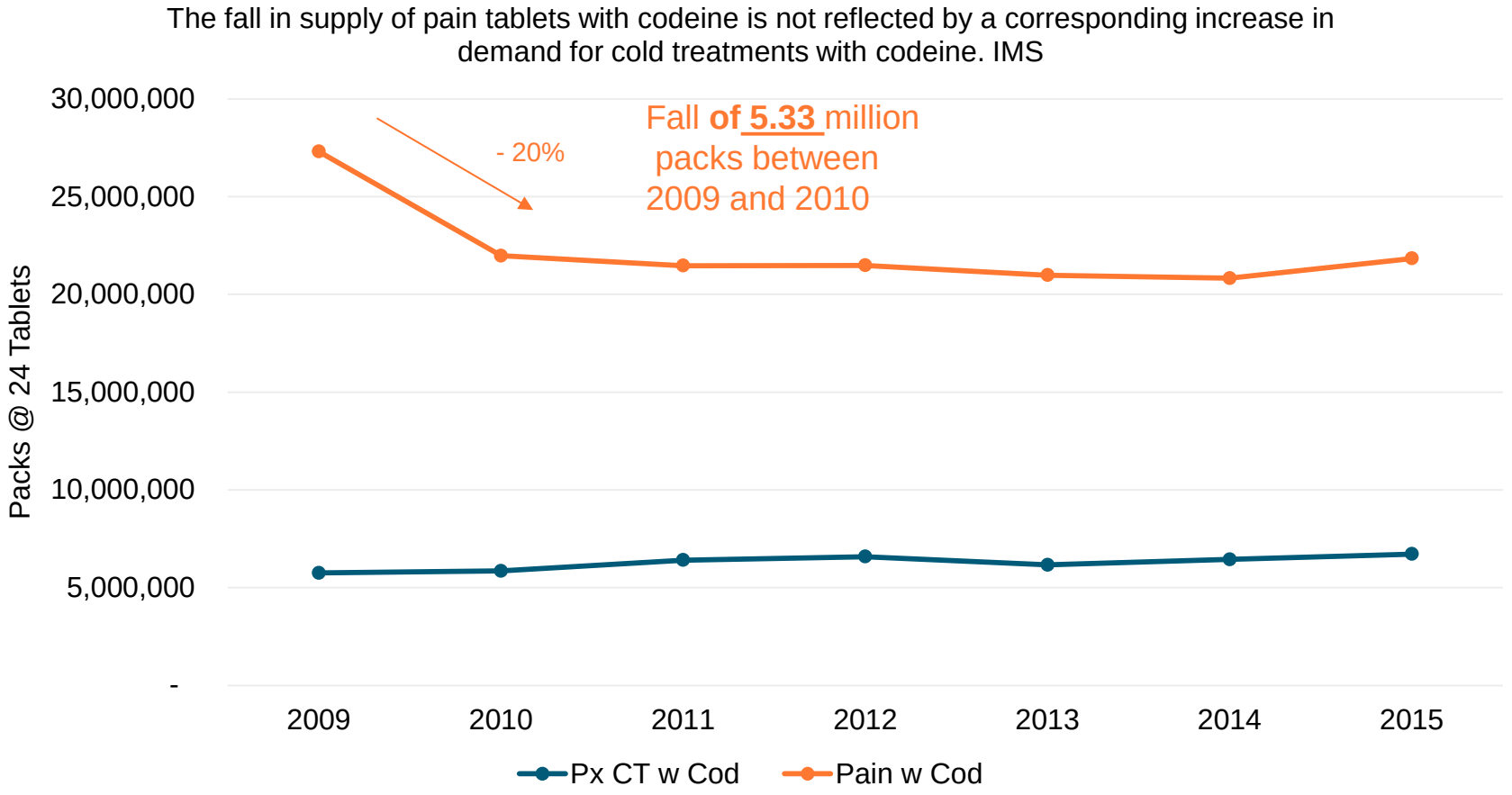
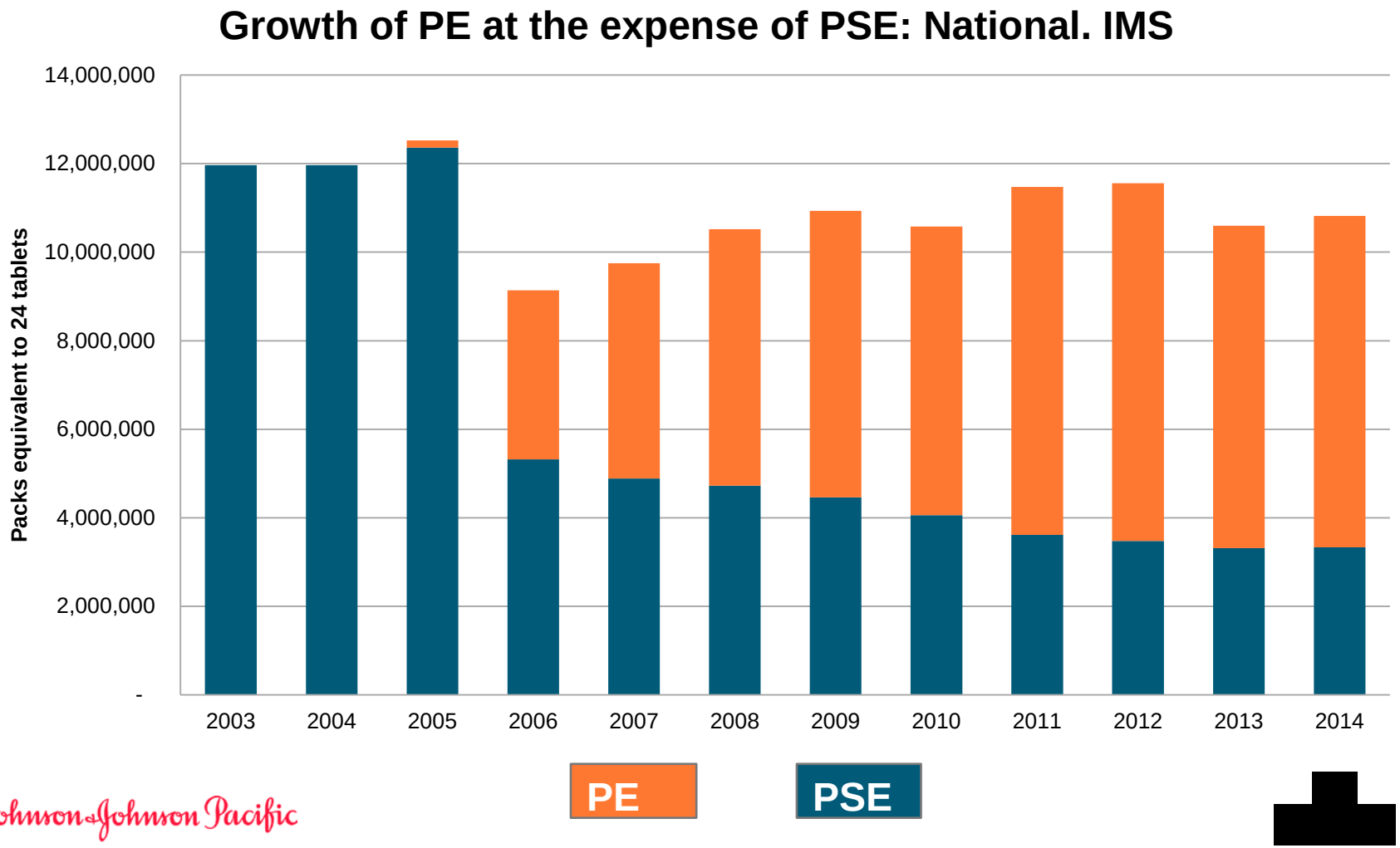
Between 2009 and 2010, the fall in supply of 5.33 million packs of pain tablets with codeine (Pain w Cod) is not reflected by a corresponding spike in demand for cold treatments with codeine.



Pseudoephedrine:
A Case Study for Codeine Analgesics?

Johnson & Johnson Pacific

The introduction of a treatment alternative (PE), plus up-schedule to S3 and meaningful pack size change, led to the reduction of PSE in pharmacy. 2/3 PE contains codeine. PE S2 with codeine was a PSE defence decision.



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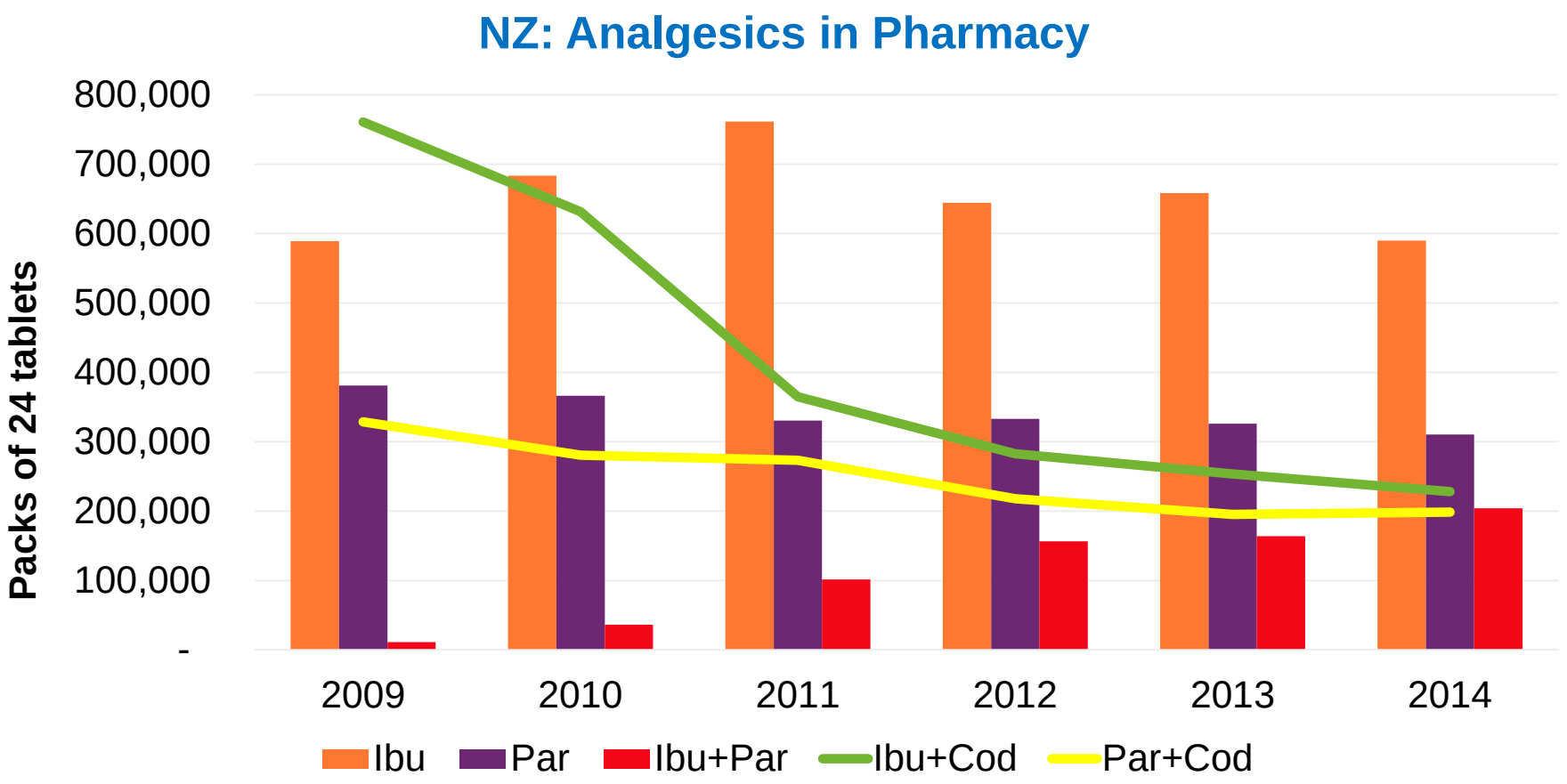
Success of Pseudoephedrine Scheduling

- Supply & demand has significantly reduced because of:
  - Up scheduling of Pseudoephedrine *(reducing access)*
  - Reduction in pack sizes *(restricting bulk purchase)*
  - Introduction of Project stop *(patient/consumer inconvenience, better tracking of pseudo shoppers)*
  - More accessible therapeutic alternative *(Phenylephrine)*

Initially S2 then unscheduled, the low scheduling of Ibu/Para combinations has facilitated the growth of these products in NZ *(analogous to S2 PE with codeine?)*



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Based on PSE/PE in AU and Ibu/Para combinations in NZ, the down-scheduling of treatment alternatives (Ibu+Para), plus a meaningful pack size change, will accelerate the reduction of analgesics with codeine in pharmacy.

- Proportion of "IBU+Par" to "IBU + Cod" and "Par + Cod":
  - NZ = 32% in 2014
  - AU = 4% in 2015
- Proportion of "IBU+Par" in NZ to non-codeine analgesics
  - NZ = 18% in 2014
  - AU = 3% in 2015

- "IBU+Par" now S2 in AU (effective 1st June 2016). In good position to effectively compete

Parallels with Pseudoephedrine Scheduling

- Supply & demand has significantly reduced because of:
  - Up scheduling of Codeine Containing analgesics *(reducing access)*
  - Reduction in pack sizes *(restricting bulk purchase)*
  - Introduction of a real time monitoring *(patient/consumer inconvenience, better tracking of pseudo shoppers)*
  - More accessible therapeutic alternative *(IBU + Par)*

J&J believe that the proposed measures will further reduce the supply of OTC codeine analgesics through pharmacy

Potential Impact of Pack Size Change on Codeine Containing Products

Johnson & Johnson Pacific

[redacted]

Dominant proportion of codeine analgesics are supplied through packs larger than 24 tablets, but no so with cold & flu products. Therefore limiting pack size to 3 days supply will affect the majority of pain treatments resulting in a substantial fall in volume.

Proportion of tablets <u>with codeine</u> provided in pack sizes greater than 24 tablets	**'11**	**'12**	**'13**	**'14**	**'15**
Aspirin/Codeine tablets in packs > 24	31%	36%	38%	42%	45%
Paracetamol/Codeine tablets in packs > 24	52%	57%	65%	75%	**80%**
Ibuprofen/Codeine in packs > 24	82%	88%	91%	93%	**94%**
Tension Pain tablets in packs > 24	15%	27%	56%	71%	**77%**
Cold Treatment tablets with codeine in packs > 24	26%	31%	34%	38%	40%
Proportion of tablets <u>without codeine</u> provided in pack sizes greater than 24 tablets	**'11**	**'12**	**'13**	**'14**	**'15**
Aspirin Tablets in packs > 24	40%	41%	42%	42%	44%
Paracetamol Tablets in packs > 24	51%	51%	57%	63%	**66%**
Ibuprofen Tablets in packs > 24	64%	65%	68%	69%	**70%**
Cold Treatment tablets without codeine in packs > 24	24%	25%	27%	31%	32%

[redacted]

Potential impact of pack size reduction of codeine containing analgesics and cold & flu products in pharmacy

Analgesics

- Increase in small packs
- Repeat purchase exposure to pharmacist – improved QUM
- Increase in cost to consumer due to repeat purchase and small packs vs larger packs price per tablet
- Heightened consumer awareness of risk/benefit of codeine analgesics. Motivate for alternative?

Cold & Flu Products

- Loss of family size cold treatment packs
- Increase cost to consumer

Observations / Conclusions

- The benchmark year of 2009 for cold & flu treatments is appropriate because of market disruption and supply issues between 2005 and 2009

- Demand for analgesics with codeine is not transferred to cold treatments with codeine when restrictions are placed on the analgesics.

- Supply of cold & flu treatments remains steady and is **below population growth**. Products with codeine match in volume those without codeine and do not reflect patterns of misuse

- The sales data clearly demonstrates that the reduced accessibility of codeine analgesics, has not seen a transfer in demand to codeine containing cold & flu products.

Observations / Conclusions

- Pack size reduction of analgesics and down–scheduling of “Ibu+Para”, along with the other measures is highly likely to reduce the amount of OTC codeine analgesics supplied through pharmacy.

- Regulatory changes will ensure that consumers requesting codeine containing analgesics will interface more frequently with pharmacists

- Consumers with families will be impacted the most with the loss of family pack sizes of cold treatments with codeine.

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Attachment 3
JJP Submission to the ACMS on Codeine rescheduling
January 2016

JOHNSON & JOHNSON PACIFIC PTY LIMITED ABN. 73 001 121 446
45 JONES STREET, ULTIMO NSW 2007, AUSTRALIA. TELEPHONE: 131 565, FACSIMILE: (02) 8260 8109
ADDRESS ALL COMMUNICATIONS TO: LOCKED BAG 5, BROADWAY, NSW 2007

Johnson & Johnson Pacific

Wednesday 27th January 2016

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. Proposed amendments referred by the delegate for scheduling advice on Codeine for consideration by the Advisory Committee on Medicines Scheduling (ACMS), March 2016

Johnson & Johnson Pacific (JJP) is pleased to be invited to provide comment on the scheduling proposals for codeine to be considered by the ACMS during the March 2016 meeting.

JJP is the sponsor of both Pharmacist Medicines (S3) and Pharmacy Only Medicines (S2) that contain codeine, in combination with paracetamol and either pseudoephedrine (PSE) or phenylephrine (PE). These products are indicated for the relief of symptoms associated with colds and flu under the brand name of Codral, a local brand that can only be found in Australia and New Zealand.

JJP is not a sponsor of analgesics and do not supply either single component or multi-component analgesics in Australia or New Zealand.

Information provided to the ACMS and delegate in May 2015 and in October 2015 remain relevant. For ease of review, these have been provided as Attachments 1 and 2.

Scheduling Proposals for Codeine

Schedule 2 (cough and cold medicine preparations):

a. Proposal to amend the Schedule 2 entry to reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction; OR
b. Proposal to up-schedule the Schedule 2 entry to Schedule 3 and reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction; OR
c. Retain the interim decision to up-schedule to Schedule 4.

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

a. Proposal to amend the Schedule 3 entry to reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction; OR
b. Retain the interim decision to up-schedule to Schedule 4.

JJP's Position

JJP is pleased to see that the scheduling of codeine is now being considered more appropriately in the context in which it is used. Below summarises JJP's position:

- JJP would like to recommend that the reference in the scheduling proposal of "cough and cold medicine preparations" is changed to "cold and flu medicine preparations". As "cough" is not an OTC indication for codeine
- JJP maintain the position that the evidence shows that there is no abuse or misuse of codeine containing cold and flu products and will continue to actively monitor the situation
- JJP supports the proposal for maintaining the S2 scheduling of codeine containing cold and flu products when supplied with new label warnings as proposed. Whilst questioning the impact, JJP does not oppose limiting the pack size to no more than 3 days supply.
- JJP strongly opposes other scheduling proposals for codeine containing cold and flu products.
- JJP supports the proposal to maintain the S3 scheduling of codeine containing analgesics limited to 3 days' supply with the additional label warnings as proposed.
- JJP's support of the S3 scheduling proposal for codeine containing analgesics is contingent on the introduction of a real time monitoring systems that has been proposed by ASMI
- JJP recommends that a well-designed, scientifically robust, Australia wide study on mortality rates associated with codeine misuse/abuse in OTC products, pre and post all codeine related scheduling decisions and other implemented measures (such as a real time monitoring system) be undertaken to determine the success of these measures in a systematic and accurate manner.

Details supporting JJP's positions are provided below.

Changing *"cough and cold medicine preparations"* to *"cold and flu medicine preparations"*

Historically codeine containing cold and flu products have been referred to as codeine containing *cough* and cold products. We would like to highlight the fact that "cough" is not a TGA approved OTC indication for codeine containing medicinal products intended to provide temporary relief from the symptoms of cold and flu.

We believe that it would be confusing and inappropriate to continue to refer to these products as "*cough and cold medicine preparations*". Similarly as these products are indicated for the temporary relief of the symptoms of cold and flu, it is equally confusing and inappropriate to refer to treatment

Therefore we recommend that any entry in the SUSMP referring to Codeine is changed from:

CODEINE *in preparations for the treatment of coughs and colds when:*

To

CODEINE *in preparations for the symptomatic relief of colds and flus when:*

Evidence of No Abuse or Misuse of Codeine Containing Cold and Flu Products

In the 2009 foreshadowing of up-scheduling and pack size reduction of OTC pain tablets containing codeine to be implemented in May 2010, the NDPSC made the considered decision not to up-schedule cold treatments containing codeine. This decision was based on their finding that there is no evidence to support the notion that cold treatments containing codeine were being misused. It should be noted that this decision was taken after a 12 month review by the Committee.

At the time, the NDPSC raised the question "by restricting access to pain tablets containing codeine through up-scheduling to S3, would there be a corresponding shift in demand towards cold tablets with codeine, as theoretically these would be easier to access by remaining S2?"

It is important to emphasise that the NDPSC was only concerned about the potential for an upsurge in demand for cold and flu treatments containing codeine as a consequence of pain treatment up-scheduling. Their concern was **not** about current misuse or abuse of these products. Since then, there has been no change in the pattern of demand for codeine containing cold and flu treatments. The NDPSC clearly made the correct decision, and knowing their concerns allowed JJP to monitor the situation. Unfortunately there was no opportunity for sharing this data with the currently advisory committee.

Evidence supporting the reduction in demand of codeine containing analgesics has not affected cold treatments containing codeine is provided in the follow pages. This evidence is from substantial data bases (IMS, AZTEC) and data presented here is limited to supporting the above point.

In the Delegate's interim decision relating to Codeine, it is stated that the ACMS' recommendation was based on numerous points, including that the OTC sales data are incomplete. We respectfully invite the Delegate to approach J&J Pacific should there be further specific questions relating to the data.

Data Sources and History

- **IMS Health – Product supplied to all pharmacies across Australia:** data obtained from all Pharmaceutical Wholesalers and most of the direct supply by manufacturers to pharmacy (feedback from IMS). This represents supply of c. 95% of all pharmaceutical products to pharmacy in Australia. Data includes special offers, discount deals etc.
- **AZTEC** – Scan data supplied by all major grocery outlets to AZTEC.
- J&J holds historic IMS and AZTEC data for the Cold Treatment market, from 2007 to 2015.
- Data for the Pain Treatment sector is only available from 2009 and is limited to Pharmacy Only. This is because J&J Pacific is not active in the OTC Pain sector and has had no reason to monitor IMS prior to 2009, nor purchase grocery data. As a subscriber to IMS, 5 year historic data is available for all therapeutic categories.

Data Analysis

- The analysis has been limited to solid dose formats e.g. tablets, capsules, gel-caps etc. This is because the issue facing the Scheduling Committee and Delegate is fundamentally an issue pertaining to the reporting of inappropriate supply of solid dose products containing codeine.
- Pack sizes vary widely across different brands and treatment categories. The data is represented as the equivalent number of packs of 24 i.e. a pack of 48 tablets is equivalent to 2 packs of 24.
- In order to create an analysis that is comparable and to provide a true perspective of the volume of product supplied across all brands and pack sizes, this "Like for Like" analysis has been performed. All brands across all Sponsors are represented and not limited to J&J.

Legend & Abbreviations

The following pages include data relating to the sales of codeine containing cold and flu products and codeine containing analgesics. The terms used within the graphical representations are provided in Table 1.

Table 1: Terms used within graphical representation of sales data for codeine containing products.

Abbreviation	Definition
Px	Pharmacy
CT	Cold Treatments
Gr	Grocery
Cod	Codeine
w	with
w/o	without
vs	versus
Pain	Analgesics - pharmacy supply (tablets)
Pain w/o Cod	Single ingredient ibuprofen, paracetamol and asprin tablets, and multi-ingredient non-codeine analgesics
Asp/Cod	Aspirin with codeine
Par/Cod	Paracetamol with codeine
Ibu/C	Ibuprofen with codeine
Tens	Multi ingredient analgesic with codeine usually indicated for 'tension pain' (e.g. Mersyndol)

Sales Trends for Cold and Flu Products 2007 – 2015 (IMS, AZTEC, MAT 2007 to 2015 inclusive)

Since 2009 there has been a general trend for pharmacy to supply cold treatments containing codeine above those without codeine (Figure 1 and Figure 2). It is apparent that this trend started in 2009 at the same time as non-pharmacy retailers began competing with pharmacy with the introduction of the unscheduled solid dose phenylephrine range of products. The volume of loss of cold and flu products without codeine from pharmacy is directly proportion to the gain in grocery (Figure 3).

When the total sales of codeine-free cold and flu treatments in both pharmacy and grocery are compared with pharmacy and the sales of codeine containing cold and flu products, the combined supply trend for each product group is close to equivalent. There is no sudden or unexplained surge or separation in demand in favour of cold treatments with codeine through pharmacy (Figure 4).

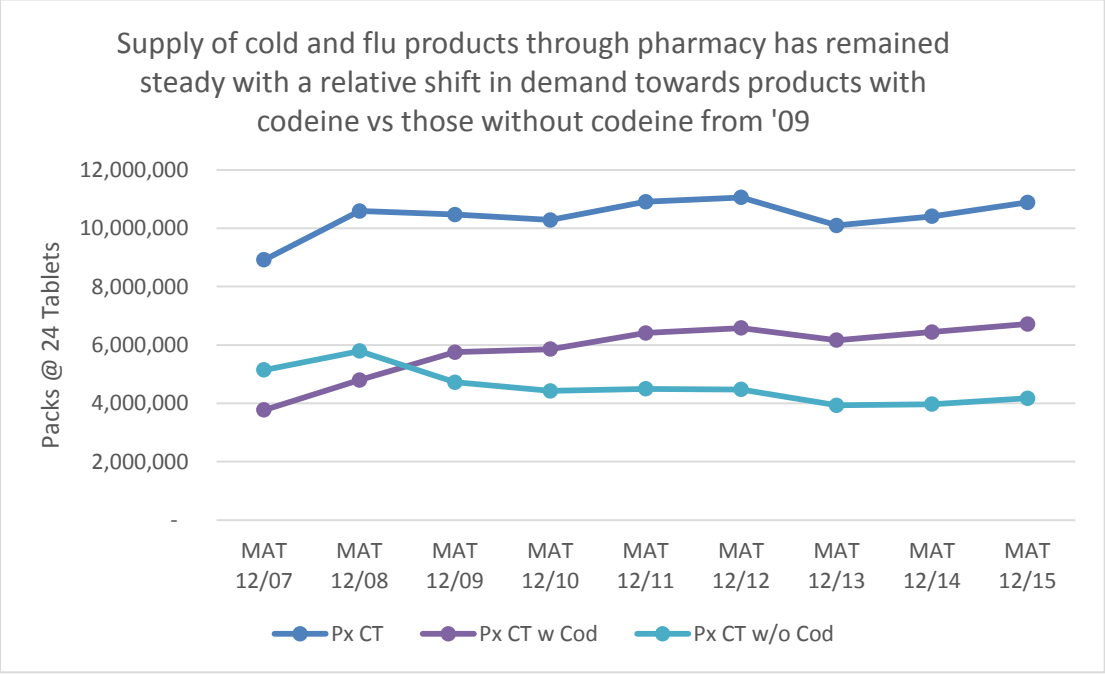

Figure 1 There is a general trend for pharmacy to supply cold and flu products containing codeine above those without codeine. This graph represents the supply of total cold and flu products through pharmacy for each 12 months from 2007 to 2015 (Px CT). This trend is evident from 2009 onwards. This trend started in 2009 as non-pharmacy retailers began competing with pharmacy with the introduction of the unscheduled solid dose phenylephrine range of products.

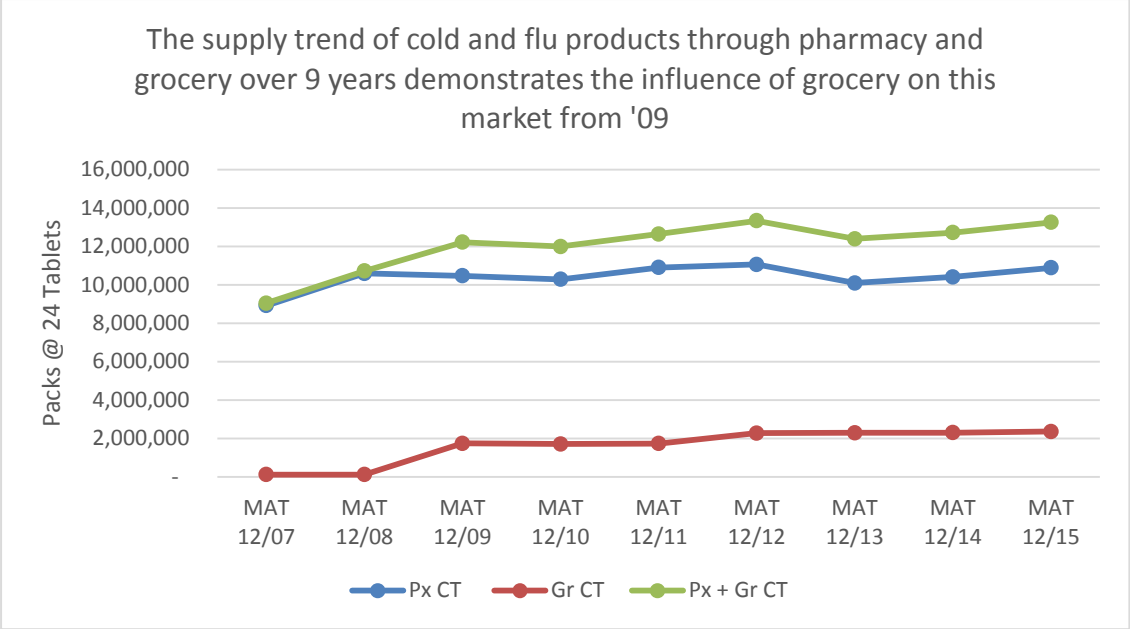

Figure 2 represents the total volume of cold and flu products supplied through pharmacy, and introduces cold and flu products supplied through grocery (Gr CT). Prior to 2009, the supply of cold and flu products through grocery was minor but with the introduction of the general sale solid dose phenylephrine range of products, grocery started actively competing for this market with pharmacy. Pharmacy cold and flu products (Px CT) has since stabilised and growth of the total sector (Px + Gr CT) is purely due to expansion in grocery.

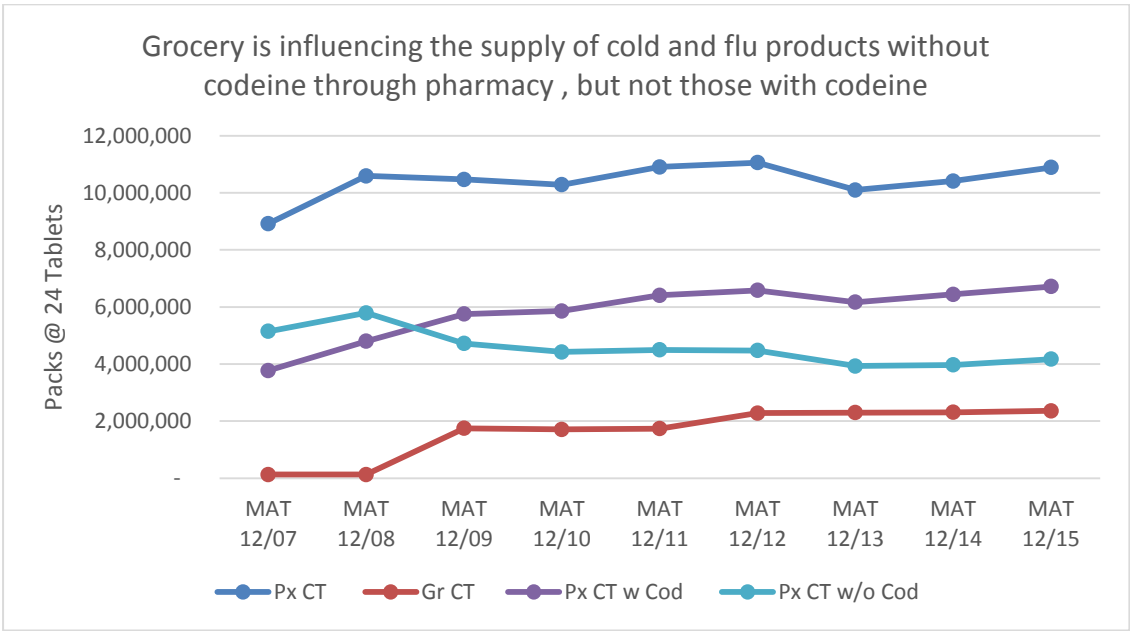

Figure 3 Graphic representation showing how the growth of the grocery cold and flu sector (Gr CT) has had a direct negative impact on supply of cold and flu products without codeine (Px CT w/o Cod) in pharmacy. The volume of loss of cold and flu products without codeine from pharmacy is about in direct proportion to the gain in grocery.

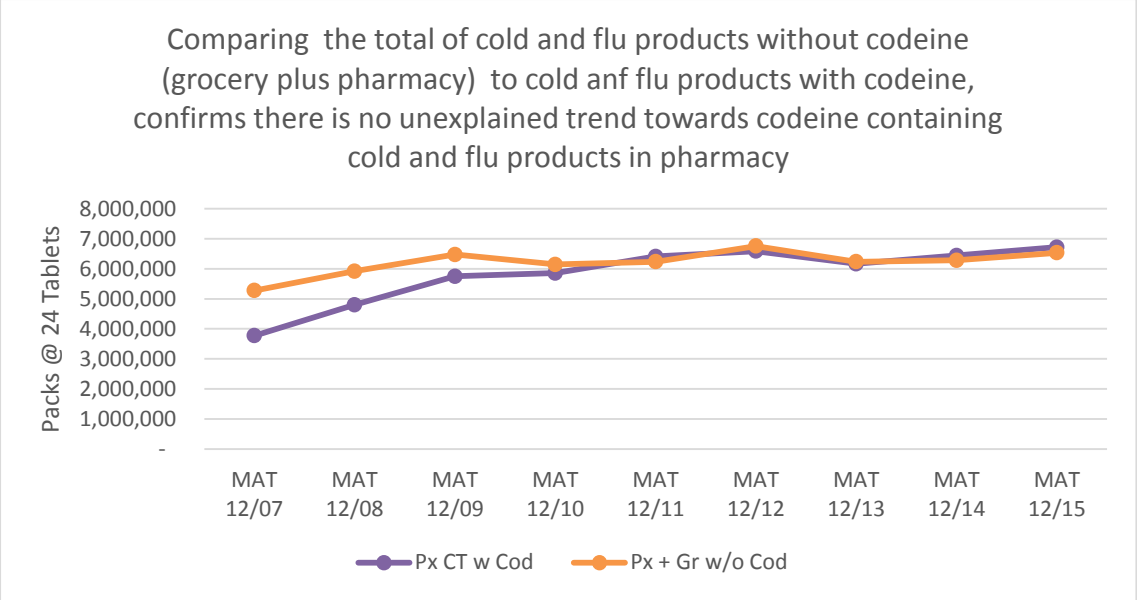

Figure 4 demonstrates that when combining the sales of pharmacy and grocery cold treatments without codeine (Px + Gr w/o Cod), and compare this with the sales of codeine containing cold treatments (Px CT w Cod), the combined supply trend for each product group is close to equivalent. There is no sudden, or unexplained surge or separation in demand in favour of cold treatments with codeine through pharmacy (Px CT w Cod).

Sales Trends of Analgesics 2009 – 2015 (IMS, MAT 2009 to 2015 inclusive)

There has been a sharp decline in codeine containing analgesics with a decrease of approximately 5 million packs in annual demand between 2009 and 2010. This fall in volume has been sustained through to 2015 (Figure 5). Interestingly, the decrease in demand of codeine containing analgesics has seen a strong increase in demand for codeine free analgesics (Aspirin, Ibuprofen, Paracetamol or non-codeine combination analgesics. All other single active analgesics {e.g. naproxen or mefenamic acid} have been excluded).

Ibuprofen with codeine is the only codeine containing analgesic product that continues to experience a strong decline in sales. Paracetamol with codeine has started to increase slightly, but this is likely to be gaining from this decline. Demand for any of codeine containing analgesics remains well below the levels of demand seen in 2009.

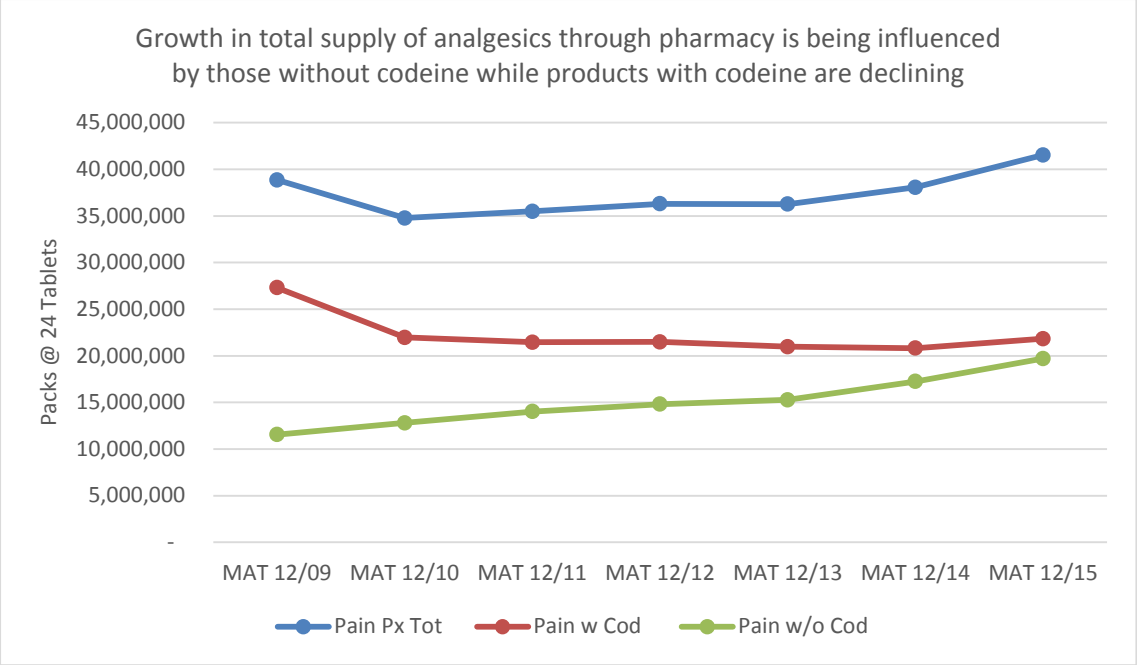

Figure 5 graphically represents the total pain treatment solid dose sector through pharmacy (Pain Px Tot). There has been a sharp decline in pain treatment with codeine (Pain w Cod) – approximately 5 million packs between 2009 and 2010. This fall in volume has been sustained through to 2015. However the sector has been supported by a strong increase in demand for pain products without codeine (Pain w/o Cod) resulting in overall growth of the pain treatment sector in pharmacy. Pain without codeine include single ingredient paracetamol, ibuprofen, aspirin, and non-codeine combination analgesics.

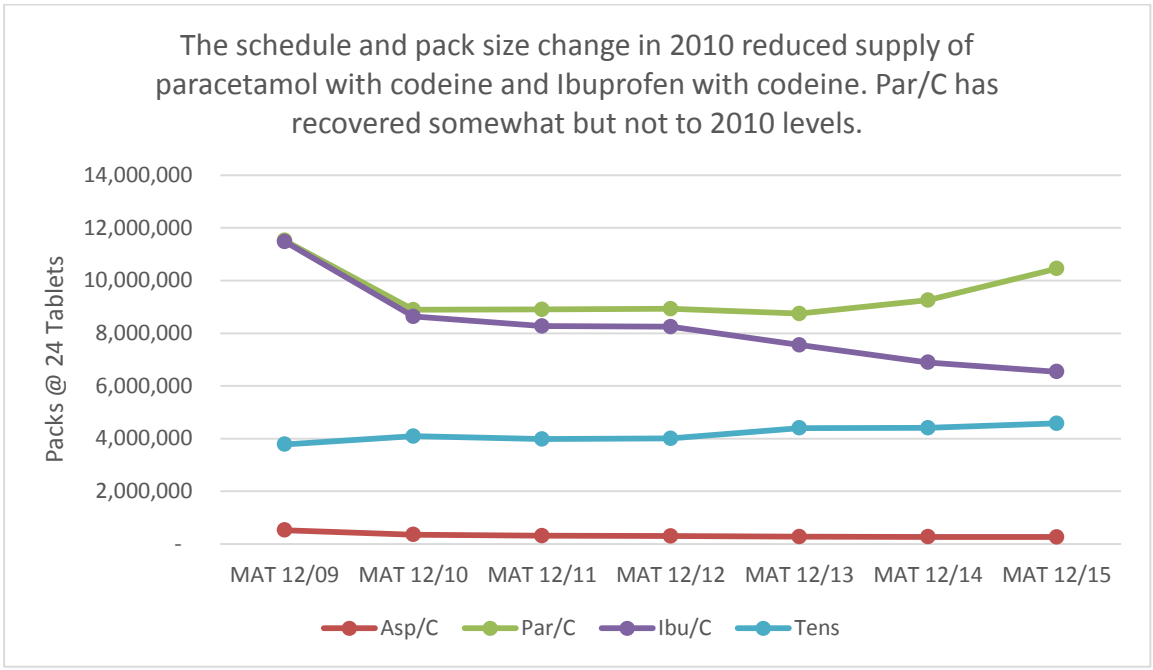

Figure 6 graphically represents the performance trends of the individual codeine containing analgesics (aspirin with codeine –Asp/Cod; paracetamol with codeine – Par/Cod; ibuprofen with codeine – Ibu/Cod; Tens – multi-ingredient pain product with codeine plus doxylamine – usually indicated for 'tension pain', e.g. Mersyndol). Ibuprofen with codeine is the only product that continues to decline strongly. Paracetamol with codeine is likely to be gaining from this decline, however has not reached 2009 levels. Figure 5 shows that in 2015 total analgesics with codeine remain below 2010 levels.

Comparison of Sales Trends of Codeine Containing Cold & Flu products and Codeine Containing Analgesics in Pharmacy (IMS, MAT 2007 to 2015 inclusive)

Between 2009 and 2010 there was a decline of approximately 5 million packs of analgesics with codeine. The trend from 2007 to 2015 for codeine containing cold and flu products has remained relatively flat, with no increase in demand at the time of or after the up-scheduling of codeine containing analgesics (Figure 7). There is no cross-over in supply between the pain and cold categories further confirming that these market sectors behave independently of each other.

Potential for cross-over in demand between pain with codeine and cold treatments with codeine: Conclusion

The NDPSC expressed some concern about a potential for an increase in demand for cold treatments with codeine as a result of scheduling and pack size change to codeine containing analgesics. Through sales date trend analysis it is clear that there has been no change in demand for codeine contain cold and flu products. This clearly shows that the concern of a transference of abuse or misuse of codeine did not occur and there is no cross-over in demand between these two sectors.

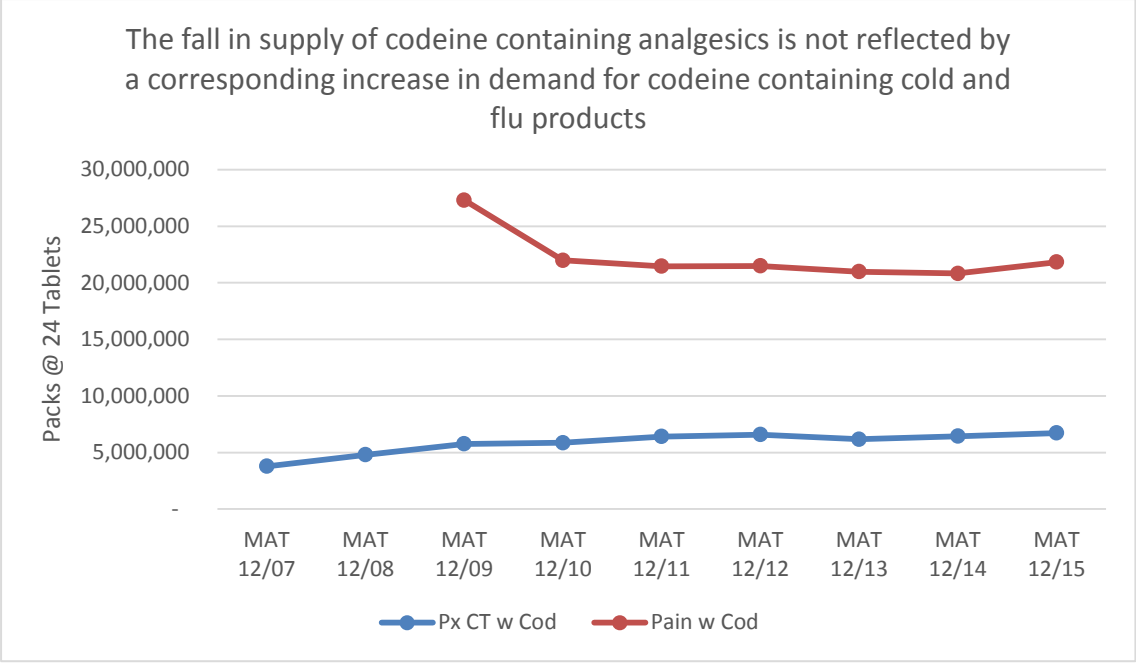

Figure 7 shows the loss between 2009 and 2010 of about 5 million packs of analgesics with codeine (Pain w Cod) from pharmacy, and the trend from 2007 to 2015 for codeine containing cold and flu products (CT w Cod). There is no increase in demand of codeine containing cold and flu products at the time of or after the up-scheduling of codeine containing analgesics. The graph demonstrates that there is no cross-over in supply between the pain with codeine and cold treatment with codeine sectors. It clearly demonstrates that these market sectors behave independently of each other. (Note that IMS data pertaining to the pain sector is not available prior to 2009).

Adverse Event Data
As previously highlighted in the submission of May 2015, Approximately 21 million packs of Codral (24 dosage units) were sold the period between January 2010 and April 2015 (equating to approximately 500 million individual dosage units and an average of 3.8 million packs per year).

During this same period JJP has recorded a total of 3 ***suspected*** cases of abuse (not confirmed). What cannot be concluded from the information held by JJP is whether the abuse is directly related to the codeine content, as the verbatim does not indicate this in two out of the three cases.

- **Case One**: An individual, reported to be an ex-smoker who excessively used cold and flu medication (not only Codral) including non-codeine containing products. The role of codeine in this instance has not been determined.
- **Case Two:** An individual felt that when they stopped taking Codral, their cold and flu symptoms retuned. The role of codeine in this instance has not been determined.
- **Case Three:** Reported via social media, a consumer stated that "I abuse your product" - no further details (including actual product) were reported and no further contact with the consumer could be made. The role of codeine in this instance has not been determined.

Conclusion
There is evidence that there has been no transference of abuse or misuse from codeine containing analgesics to codeine containing cold and flu products. Sales trends for codeine containing cold and flu products remain unchanged when compared to the demand prior to the up scheduling of codeine containing analgesics in 2009.

In the public submissions made in response to the call for public comment for the scheduling of codeine, there was no cold and flu products containing codeine implicated in any of the medicine misadventures reported, therefore there is no evidence to warrant a change to the scheduling of these products.

This is further supported by the fact that, significant volumes of codeine containing cold and flu products are distributed annually by JJP. During the last 5 years, JJP have received a total of three, unconfirmed cases of abuse or misuse.

Consumers are using the codeine containing cold and flu product responsibly and as directed. There is evidence of no abuse and as such, the current scheduling remains appropriate.

JJP's Position: There is evidence of no abuse or misuse of codeine containing cold and flu products, which justifies the recommendation to maintain the current scheduling (S2) for codeine containing cold and flu products.

Maintain S2 entry of codeine containing cold and flu products when limited to 3 days' supply.

There is no valid or scientifically robust reason or argument that would justify the re-scheduling of codeine containing cold and flu products.

There is evidence that demonstrates that there is no harm, abuse or dependency associated with codeine containing cold and flu preparations. The risk/benefit profile of codeine containing cold and flu preparations has not changed since the NDPSC decision in 2009 which deemed the currently scheduling as being appropriate.

The NDPSC previously determined that the S2 entry for codeine-containing cold and flu products was appropriate for the following reasons:

1. Symptoms of pain can be acute and or chronic, potentially leading to long-term use of OTC analgesic products. Conversely, symptoms associated with colds and flus are episodic and self-limiting, therefore unlikely to lead to inadvertent codeine addiction. Consumers are less likely to dose escalate or self-treat with cold and flu products for extended periods of time, mitigating any potential for misuse as is reported with codeine-containing analgesic products.
2. Cold and flu products containing codeine often have multiple therapeutically-active ingredients and these, together, might diminish abuse/misuse.
3. Reported misuse of cold and flu products containing codeine is extremely rare and no submissions asserted that there was evidence indicating a problem.
4. Evidence was provided suggesting that when PE codeine combinations are not available (due to an out of stock situation), pharmacy sales of PSE products escalated. The continued availability of PE/codeine-combination products as S2 was considered appropriate given the major concerns relating to the illicit diversion of pharmacy-originated PSE. The concern of PSE diversion into methamphetamine remains current.

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.

There has been no additional studies, nor 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 was addressed in the JJP submission of 7th May 2015 and updated in the above section.

Maintaining the S2 Standard for Phenylephrine-based Cold Treatment Products with Codeine - Phenylephrine as a Pseudoephedrine Management Strategy

Pseudoephedrine, obtained through pharmacy for the illicit purpose of the manufacture of methyl amphetamine (ice, crystal meth, etc), became a substantial law enforcement and social issue prior to 2006. Solid dose phenylephrine was registered for use in Australia in part as a strategy to reduce the quantity of pseudoephedrine stocked and supplied through pharmacy.

The effectiveness of this strategy can be demonstrated through the data presented in Figure 8. A limited range of solid dose phenylephrine products were introduced onto the Australian market in late 2005, while the full range of pseudoephedrine alternatives, including phenylephrine with codeine, were introduced in 2006.

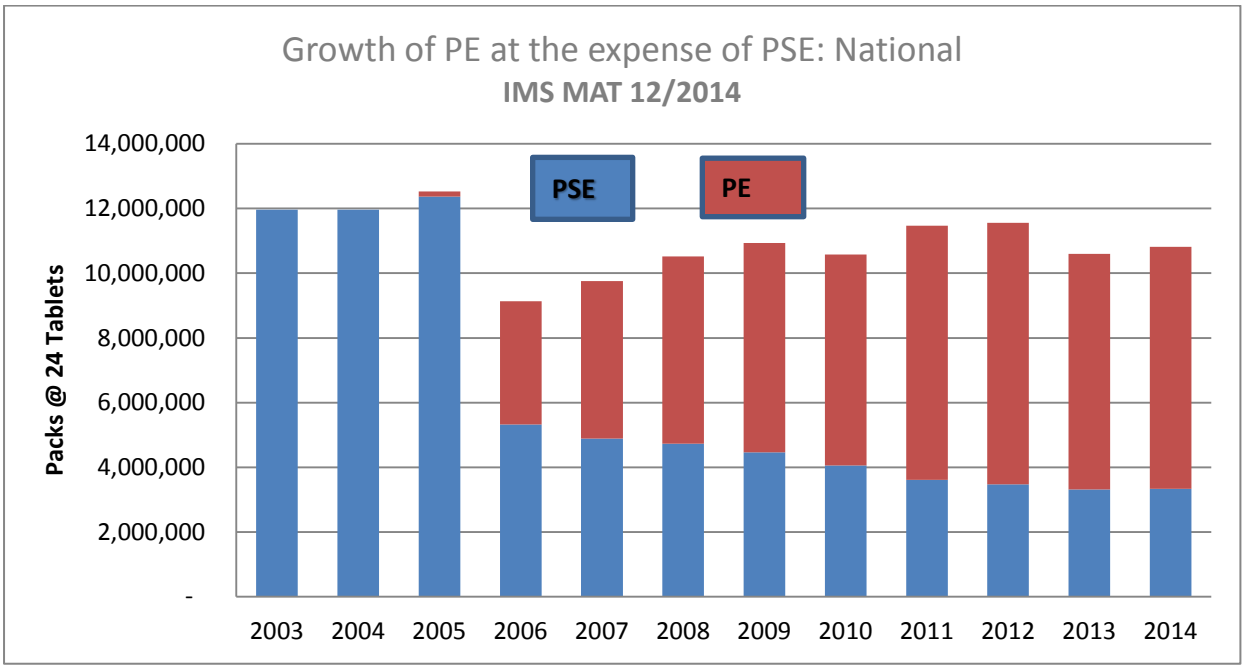

Figure 8 represents pack size equivalent of pseudoephedrine and phenylephrine based cold treatment products. After the launch in 2005/2006 of phenylephrine, followed by a schedule change to S3 for pseudoephedrine based products, the decline in volume of pseudoephedrine in pharmacy is strongly evident.

Table 2 shows that in 2015, 62% of all solid dose phenylephrine based cold treatment products contained codeine. This preference by pharmacy and consumers towards for phenylephrine products with codeine has been sustained for many years.

	2011	2012	2013	2014	2015
Proportion of phenylephrine based products containing codeine to total phenylephrine	60%	61%	62%	62%	62%

Table 2 The proportion of codeine containing phenylephrine products sold when compared with codeine free-phenylephrine combinations in pharmacy. Codeine containing phenylephrine combination products account for 60% or more of all sales of phenylephrine combination products in pharmacy**.**

All pseudoephedrine based products are schedule 3 Pharmacist Medicines. Pseudoephedrine is acknowledged to be the most efficacious of the systemic nasal decongestants.

Should codeine-phenylephrine cold and flu products be up-scheduled to S3, they will fall into the same restrictions and regulatory framework as the pseudoephedrine based products. The pharmacist

will therefore most likely lean towards recommending the more efficacious product range, i.e. pseudoephedrine, negating the effectiveness of the phenylephrine launch strategy described above. The result will be an increase in the volume of pseudoephedrine products in the supply chain as well as the quantities stored and recommended in pharmacy, increasing risk of illicit access.

Impact of limiting pack sizes to three days' supply

Limiting pack size to three days treatment will have a substantial impact on supply patterns to codeine containing OTC products, as the majority of packs supplied to consumers are from pack sizes above 24 tablets. Maximum daily dose for the majority of these tablets is 8 tablets per day (2 tablets 4 x per day).

Table 3 and Table 4 show the proportion of products with and without codeine based that are sold in pack sizes greater than 24.

These tables further cement the view that cold and flu products are very different to analgesics. Irrespective of the presence or absence of codeine in cold and flu products, packs sizes of greater than 24 dosage units account for 40% or less of all sales between 2011 and 2015.

Analgesics are very different to cold and flu products with the larger pack sizes counting for the vast majority of sales (irrespective of the presence/absence of codeine).

Table 3 Proportion of tablets with codeine provided in packs greater than 24 tablets. Packs sizes greater than 24 for Cold and flu treatments containing codeine account for less than half of all sales, where for analgesics, packs sizes greater than 24 account for the vast majority of sales.

Proportion of tablets with codeine provided in pack sizes greater than 24	2011	2012	2013	2014	2015
Aspirin/Codeine tablets in packs > 24	31%	36%	38%	42%	45%
Paracetamol/Codeine tablets in packs > 24	52%	57%	65%	75%	80%
Ibuprofen/Codeine in packs > 24	82%	88%	91%	93%	94%
Tension Pain tablets in packs > 24	15%	27%	56%	71%	77%
Cold Treatment tablets with codeine in packs > 24	26%	31%	34%	38%	40%

Table 4 Proportion of tablets without codeine provided in packs greater than 24 tablets. Packs sizes greater than 24 for Cold and flu treatments containing codeine account for less than half of all sales, where for analgesics, packs sizes greater than 24 account for the vast majority of sales.

Proportion of tablets without codeine provided in pack sizes greater than 24	2011	2012	2013	2014	2015
Aspirin Tablets in packs > 24	40%	41%	42%	42%	44%
Paracetamol Tablets in packs > 24	51%	51%	57%	63%	66%
Ibuprofen Tablets in packs > 24	64%	65%	68%	69%	70%
Cold Treatment tablets without codeine in packs > 24	24%	25%	27%	31%	32%

Limiting codeine containing products pack sizes to no more than 3 days' supply is likely to have the following consequences:

- An increase in total volume of smaller packs in pharmacy
- An increased frequency of exposure to the pharmacist for S3 products as a result of the smaller number of tablets per pack, as the customer will need to return more frequently. Additional exposure to the pharmacist for S2 products is unlikely.
- An increase in opportunity to council pain product consumers towards more appropriate treatment
- The unintended consequences of the loss of family pack sizes of cold treatments. Pack sizes of 48 tablets for cold treatments are there to provide a convenience and cost saving for families purchasing these products.

Overall, restricting packs sizes to 24 for codeine containing cold and flu products will have little benefit to the public health in Australia.

JJP's Position: JJP supports the recommendation to maintain the current scheduling (S2) for codeine containing cold and flu products. JJP has no objections to limiting pack sizes to 3 day supply.

Opposition to other scheduling proposals for codeine containing cold and flu products.

JJP opposes any changes to the scheduling of codeine containing cold and flu products, with the exception of limiting supply to a maximum of 3 days supply.

In our previous submissions (appendices 1 & 2), we highlighted the impact on the public health system should codeine containing cold and flu products be re-scheduled to Prescription only. This argument will not be repeated here, but we do request that the information provided previously be considered in the context of this decision. The environment has not changed and the data provided previously is still valid.

We would like to highlight that in the ASMI response to the interim decision, the Macquarie University Fact book estimated that the up-scheduling codeine-containing cold and flu medicines would cost the Australian economy $257 million annually. With costs borne by government due to increased doctor visits, Medicare and dispensing costs at $53 million and a further $174 million due to productivity losses caused by the restricted access. The balance of costs would be borne by consumers.

JJP's Position: There is evidence of no abuse or misuse of codeine containing cold and flu products and therefore there is no justifiable reason to implement more restrictive scheduling for these products especially given the risk/benefit ratio will not improve if this was to occur.

Supporting the proposal to maintain the S3 scheduling of codeine containing analgesics limited to 3 days' supply with the additional label warnings as proposed.

JJP does not market any single active or combination primary analgesics in either Australia or New Zealand.

We are aware there have been some case reports of adverse outcomes in some patients when excessive amounts of OTC codeine containing analgesics have been consumed as a result of codeine dependence. Codeine containing analgesics have a role to play in the self-management of acute episodes of pain and the vast majority of consumers use these products appropriately.

In no way does JJP trivialise or down-play the serious nature of the reports of medicine misadventure that might be associated with the codeine containing analgesics, however we believe that alternative measures for addressing the issue of misuse should be explored.

As members of ASMI, JJP fully support and endorse the position that has been put forward by ASMI in relation to the scheduling proposals for codeine containing analgesics. This is supporting proposal (a) for analgesics – to amend the Schedule 3 entry to reduce the pack size to not more than 3 days' supply and to also include a label warning that codeine can cause addiction.

JJP's Position: JJP supports the recommendation to amend the schedule 3 entry for codeine for analgesics to restrict the pack size to not more than 3 days' supply. JJP does not support the proposal to adopt the recommendation of the interim decision to make all codeine containing products Schedule 4.

Support of the S3 scheduling proposal for codeine containing analgesics is contingent on the introduction of a real time monitoring systems that has been proposed by ASMI and the guild

As a member of ASMI, JJP supports and recommendation by ASMI in relation to the introduction of a real time monitoring system for the sales of codeine containing analgesics only.

ASMI and the Pharmacy Guild have developed software that will provide pharmacists with a clinical and decision-making support tool. The software is to be used in together with the PSA's document "Guidance for provision of a Pharmacist Only medicine – Combination analgesics containing codeine." The document provides instructions for pharmacists to follow when deciding whether to supply OTC codeine containing analgesics for temporary relief of moderate to severe pain.

The system has been designed record and monitor sales of OTC codeine containing analgesics. Details that will be recorded include, but are not limited to:

- Customer Details
- Product supply or not
- Details of the product supplied
- Indications for supply or refusal.

This system will allow pharmacists to be able to review any other recent purchases to assist in assessing how to best manage the consumer's request. This software will identify "pharmacy shoppers" to be quickly identified and allow for the referral to an appropriate healthcare professional.

For the purposes of clarity, this is a separate initiative to Project Stop and the two systems are independent. This software is about ensuring consumers that are at high risk of medicine misadventure are identified and helped in a timely manner. Project stop is a non-mandatory tool that is utilised by relevant law enforcement agencies for identification of individuals that might be involved in criminal activity.

There are no comparable software systems in place that record or identify "doctor shoppers" who may have problems with dependence or misuse of prescription opiates. If this software proves successful, it could lay the foundations for software to address this issue.

The concept of real time recording has been proposed to help identify those consumers accessing and consuming inappropriate amounts of Schedule 3 codeine containing pain products. Recording may be appropriate for products at risk of misuse, however, including products that are not at risk of misuse will increase the complexity and administration burden of the process. Also it would be reasonable to expect a proportion of consumers to purchase more than one pack of cold treatment products – a process that would not easily fit into the recordable system.

JJP's Position: JJP supports the mandatory implementation of a real time monitoring system for the sale of codeine containing analgesics only.

Measuring Outcomes: Additional Scientifically Robust Studies

There have been some recent publications where conclusions of have been drawn about the abuse and mortality rates associated with codeine, including that "*Codeine-related deaths (with and without other drug toxicity) are increasing as the consumption of codeine-based products increases*". [1] Evidence (IMS Data) presented above categorically demonstrates that since the up scheduling of codeine containing analgesics in 2010, there has been a significant decrease in overall sales of codeine containing products, being driven by the analgesic category , and therefore there is no likelihood of increased consumption.

The studies undertaken by Pilgrim[2] and Roxborough[3] not without limitation, and a more rigorous and robust approach needs to be taken to draw any valid conclusions relating to the mortality rates associated with OTC codeine use. The publications referenced above actually open up more questions, than answers. Some of the limitations include that fact that the authors did not consider the mortality rates pre- and post- the up-scheduling of codeine containing analgesics. The studies were also limited to a small geography and are unlikely to represent the situation from a national perspective.

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

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

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

JJP recommends that a well-designed, scientifically robust, Australia-wide study on mortality rates associated with codeine misuse/abuse in OTC products, pre- and post all codeine related scheduling decisions (including previous scheduling decisions) along with the implementations of other measures (such as a real time monitoring system for codeine containing analgesics) be undertaken to determine the success of these measures in a systematic and accurate manner. This research should be independently conducted and undertaken with the utmost rigour and without bias. This research should look at all categories of codeine containing products – inclusive of cold and flu products, non-prescription codeine containing analgesics and also prescription only codeine containing medicines.

JJP's Position: JJP recommends a scientifically robust and independent study be undertaken to measure the success of the previous scheduling decisions for codeine products and any measures that are implemented as part of the current scheduling proposal relating to codeine to ensure all decisions evidence based.

Appropriate timeframes for Implementation

Irrespective of the scheduling decision for codeine containing cold and flu products or codeine containing analgesics, JJP requests that the delegate allow a sufficient implementation time for the changes to be effective. Due to supply chain and production complexities, JJP requests that if the delegate decides to make changes to the scheduling despite the data provided above, a minimum of 2 years is provided to make the transition, with an effect date following a cold and flu season (i.e. towards the end of a calendar year).

Conclusions

Data has been provided demonstrating that there is evidence of no abuse or misuse of codeine containing cold and flu products. Therefore JJP request that the delegate consider the following:

- The current scheduling for codeine containing cold and flu products remains appropriate, as there is evidence of no abuse or misuse in this category
- The schedule 2 entry of codeine is altered from "cough and cold medicine preparations" to "cold and flu medicine preparations.
- JJP believes the reduction of pack sizes to no more than 3 days supply is of limited benefit for this category however there are no objections to this request, providing sufficient time is permitted to allow transition without stock write offs.
- The proposal to maintain the S3 scheduling of codeine containing analgesics limited to 3 days' supply with the additional label warnings as proposed and implementation of a real time is appropriate but the success of these measure must be measured
- A well-designed, scientifically robust, Australia wide study on mortality rates associated with codeine misuse/abuse in OTC products, pre and post all codeine related scheduling decisions and other implemented measures (such as a real time monitoring system) be undertaken to determine the success of these measures in a systematic and accurate manner

Thank-you for this opportunity to provide comment on the scheduling proposals for Codeine. Please feel free to contact me should you need provide further data or information.

Johnson & Johnson Pacific

Appendix 1
JJP submission to the ACMS on the scheduling of Codeine
May 2015

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Johnson & Johnson Pacific

Thursday 7th May 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 meeting, July 2015

Proposal to delete the Schedule 3 entry for codeine and reschedule the current Schedule 3 codeine entry to Schedule 4 due to potential issues of morbidity, toxicity and dependence. In addition to considering the appropriateness of Schedule 2 entry of codeine

Johnson & Johnson Pacific (JJP) recognises the challenge of addiction to society; we are strongly opposed to the proposal to review the scheduling of codeine in cold and flu products for the following reasons:

1. The NDPSC determined in 2009/2010 that Schedule 2 for codeine containing cold and flu products was appropriate due to the differences in risks associated with cold and flu products versus analgesics. No evidence has emerged to suggest that the risk-benefit/Abuse/Misuse profiles have changed since this decision was made.
2. 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;
3. There is no current or historical evidence of widespread abuse of cold and flu products containing codeine;
4. 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.
5. 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, will have the perverse 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;
6. 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.

JJP is the sponsor of both Pharmacist Medicines (S3) and Pharmacy Only Medicines (S2) that contain codeine, in combination with paracetamol and either pseudoephedrine (PSE) or phenylephrine (PE). These products are indicated for the relief of symptoms associated with colds and flu under the brand name of Codral, a local brand that can only be found in Australia and New Zealand.

JJP is not a sponsor of analgesics and do not supply either single component or multi-component analgesics in Australia or New Zealand.

Executive Summary

In 2009, the now defunct National Drugs and Poisons Schedule Committee (NDPSC), voted to amend the scheduling of codeine containing analgesics from S2 to S3 based on evidence of inappropriate use. At its June and October 2009 meetings, the NDPSC confirmed that the Schedule 2 codeine entry pertaining to cold and flu products remained appropriate given there were no reports that use of these products was leading to misuse or abuse. A decision was reached maintain packs sizes equivalent to 6 days' supply and to review the scheduling cold and flu could medicines in 12 months, should evidence of misuse or abuse emerge. To date there has been no evidence of misuse or abuse in this category.

In a separate decision, all pseudoephedrine (PSE) products (including combination products) were scheduled to S3 for the distinct purpose of limiting access to PSE for illicit drug trade and conversion into methamphetamine.

Since these changes came into effect, 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 now defunct NDPSC previously expressed a concern that this may occur when codeine containing analgesics were up-scheduled from S2 to S3; however, as noted, there has been no evidence that this has occurred.

JJP wishes to raise concerns regarding the unintended consequences of scheduling changes to cold and flu products with codeine should the NDPSC's previous decision be overturned. Importantly, these changes are likely to have negative economic impacts to the patient and the public health system by unnecessarily driving cold and flu sufferers into GP clinics (or emergency rooms) 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.

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.

Evidence provided in this submission clearly supports the notion that the current scheduling of cold and flu products with codeine is appropriate and that no new evidence has emerged since the scheduling decisions in 2009 and 2010. The evidence demonstrates that this is no case for the up-scheduling for codeine containing cold and flu products.

Cold and flu products containing codeine should be excluded from any consideration of measures aimed at addressing analgesic codeine combinations. No new evidence of inappropriate use has been identified in relation to these products. 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 provided within.

Inability to Assess the Evidence Provided in Support of a Schedule Change

JJP would like to highlight that parties with a vested interest in the scheduling of codeine have not been given an opportunity to review any evidence to suggest that there is an issue that warrants the up-scheduling of codeine, especially in relation to cold and flu products containing codeine. The proposal for a review of the scheduling provides the general public with no information in relation to the issue apart from a motherhood statement of ….. **"***due to potential issues of morbidity, toxicity and dependence*".

JJP would argue that this statement in and of itself reflects no new developments in patient safety data and that the scheduling of codeine containing medicines has always been based on the ingredient's known risk-benefit profile.

In the interest of procedural fairness, JJP believes that any evidence submitted in support of the up-scheduling proposal should be made publically available for consideration by interested parties. Comments to this effect were included in the Johnson & Johnson Family of Companies submission to the expert panel's review of the current medicine and medical device legislation.

JJP would like to request that the ACMS consider deferring any recommendation in relation to the scheduling of codeine and requests that all evidence relating to "*the potential issues of morbidity, toxicity and dependence*" are published in the public domain for critical analysis by those with a vested interest in codeine.

Interested parties cannot be reasonably expected to provide a considered and complete submission addressing any issues raised in the original proposal, without being given the opportunity to review the evidence.

Furthermore, given the impact on the consumer of up-scheduling a commonly used product i.e. driving them into a new care setting where a waiting time and a co-payment is possible, this change should be subject to a period of broad public consultation to avoid a justifiable consumer backlash. In addition,

the Department of Health and Aging has a public obligation to model the impact on the health budget as a result of driving people who currently self-care into General Practice and Emergency Departments.

JJP urges the ACMS to consider these additional obligations before making any changes to the current scheduling arrangements for codeine.

Primary Issue is Limited to OTC Codeine-Containing Analgesics

JJP has been led to (anecdotally) understand that the primary issue motivating the inclusion of a change to the schedules containing codeine on the ACMS agenda is the small number of reported cases of misuse of S3 analgesics that contain codeine. This misuse might result in severe adverse events (AEs), mostly gastrointestinal, renal or hepatic injury. These AEs are believed to be the result of excessively high doses of ibuprofen or paracetamol consumed as a result of drug seeking behaviour for the codeine content of these products.

Media reports on the 25th and 26th April 2015 stated that researchers at Monash University have reported an increase in codeine abuse. This was based on a letter to the editor of the Medical Journal of Australia authored by Pilgrim *et al* 2013[1] (Appendix 1). The work conducted by Pilgrim *et al*, looked at post-mortem results from the period of 1 January 2001 to 31 December 2011. The decision to up-schedule codeine containing analgesics became on the 1st May 2010, at which time there was a significant drop in sales/demand/supply of codeine containing analgesics. **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.

To determine whether the up-scheduling of codeine containing analgesics has had a real impact, the work conducted by Pilgrim *et al* should be conducted again, on a national scale looking at data both pre- and post- the up-scheduling of codeine containing analgesics. This would give a true indication as to whether there is a trend of increased codeine abuse in Australia and whether the up-scheduling of codeine containing analgesics has been successful at addressing the issue.

Given the ramifications of further restrictions (discussed later), any recommendation should be based on real, evidence submitted in a peer-reviewed publication of the current situation and not data collected prior to the effective date of the former NDPSC's re-scheduling decision. It is bad policy to base a change of this potential magnitude on anecdotal evidence submitted around a small number of difficult cases.

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

Again, JJP wishes to emphasise that excessive consumption behaviour towards cold and flu products containing codeine has not been reported, nor previously considered as a consumer risk issue, when the past NDPSC reviewed and deliberated on the appropriate scheduling of OTC codeine containing products in 2009/10.

2009/10 NDPSC Scheduling Decision of Cold and Flu Products

In 2009, the NDPSC confirmed that the S2 scheduling of codeine-containing cold and flu products was appropriate. For reasons previously stated regarding the S3 scheduling of PSE products, this decision was made on the proviso that phenylephrine (PE) was always included in the formulation.

Pack sizes were maintained at no more than 6-days' supply based on status quo at the maximum dose recommended on the label allowing for a family pack size of 48 tablets. This pack size was deemed to be appropriate by the panel members as it was recognised that colds and flu are easily transmitted among household members.

Main reasons why the continued S2 listing of codeine-containing cold and flu products was deemed appropriate by the NDPSC:

1. Symptoms of pain can be acute and or chronic, potentially leading to long-term use of OTC analgesic products. Conversely, symptoms associated with colds and flus are episodic and self-limiting, therefore unlikely to lead to inadvertent codeine addiction. Consumers are less likely to dose escalate or self-treat with cold and flu products for extended periods of time, mitigating any potential for misuse as is reported with codeine-containing analgesic products.
2. Cold and flu products containing codeine often have multiple therapeutically-active ingredients and these, together, might diminish abuse/misuse.
3. Reported misuse of cold and flu products containing codeine is extremely rare and no submissions asserted that there was evidence indicating a problem.
4. Evidence was provided suggesting that when PE codeine combinations are not available (due to an out of stock situation, for instance), pharmacy sales of PSE products escalated. The continued availability of PE/codeine-combination products as S2 was considered appropriate given the major concerns relating to the illicit diversion of pharmacy-originated PSE.

The concern of PSE diversion into methamphetamine remains current.

[redacted]

[redacted]

Monitoring of S2 Codeine-Containing Cold and Flu Products

When the former NDPSC confirmed the S3 scheduling of codeine-containing analgesics, questions were raised over whether this would potentially lead to a surge in demand for S2 codeine-containing cold and flu products. It was noted by the NDPSC that this should be monitored.

The NDPSC was disbanded after the scheduling decisions were made for codeine and as a result, no formal requests were ever made to revisit the issue.

However, acknowledging its role as a major supplier in the cold and flu category, JJP 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 and with the Chief Pharmacist of the NSW State Department of Health. Data specific to New Zealand will similarly be shared with Medsafe and other key stakeholders (June 2015). There are plans for JJP to share its data more widely with other key stakeholders.

Both the national and state data conclusively demonstrates 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).

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.

[redacted]

Unintended Consequences Relating to Rescheduling of Cold and Flu Products with Codeine

Increase of Pseudoephedrine in Pharmacy & Supply Chain

In the situation where PE products with codeine are rescheduled to S3, both PE and PSE products would be required to be stored behind the dispensary and supplied only upon consultation with the pharmacist. This would have the effect of a three-fold increase in the volume of product stored behind the counter - based on 2014 figures, an additional 4.7 million packs (all brands, not just JJP brands).

With both PE and PSE scheduled as S3, pharmacists will be more likely to choose or prefer the recommendation of PSE for effective relief of cold symptoms, given its superior efficacy when compared with phenylephrine.

This has been the pharmacists approach since 2006 with the rescheduling of PSE based products to S3. If S2 codeine containing cold and flu products were to be up-scheduled it would exponentially increase the volume of PSE products in pharmacy, and the associated risks related to illicit access for methamphetamine manufacture. JJP can confidently make this claim as we saw a significant increase in the demand of PSE-containing Codral when there were supply issues with PE-containing Codral. The original and **successful strategy** that was supported by the NDPSC to help reduce the volume of PSE supplied through pharmacy by maintaining the S2 scheduling of PE with codeine combinations.

To make a decision that would drive the growth of pseudoephedrine is not in the interest of public health.

If an additional move was made to make the Codeine PSE combinations S4, based on the research conducted at Macquarie University (see below), it will drive consumers to their GPs (as noted above) for prescriptions of pseudoephedrine with codeine, but it may well encourage criminals to go doctor shopping for PSE prescriptions as a means of obtaining precursor material for the manufacture of methamphetamine and the associated harm to the community. The ability to track PSE doctor shopping behaviour is limited as it would be private prescription, and will not get captured in project STOP.

Increased Burden on the Public Health System

Recent Macquarie University research has revealed that 62% of people would visit a doctor if the medication for their condition became unavailable over the counter[2] (Appendix 2). Rescheduling S3 cold and flu products with codeine means that a major proportion cold and flu products containing PSE will become S4 prescription medicines

If those 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 (supported further below).

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.

At a time when the Federal Government has been desperate 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.

Increase to Inappropriate Prescribing of Antibiotics

It is widely accepted that General Practitioners have not yet managed to reign in the magnitude of antibiotics prescribed for colds and flus. Australia has one of the highest prescribing rates of antibiotics for acute viral upper respiratory tract infections. If access to codeine containing cold and flu products was further restricted by up-scheduling, it is highly likely that there would be an increased number of patients presenting to GPs with colds and flus. It is also highly likely that there would be

[2] Macquarie University. The Value of OTC Medicines in Australia. March 2015

an increased number of antibiotics prescribed, as a result of driving people into this setting of care. The inappropriate use of antibiotics for the treatment of colds and flus is an area NPS Medicinewise (the National Prescribing Service) is actively trying to address; due to the detrimental impact antibiotic resistance has on public health.

Shifting the Problem from Pharmacists to General Practice

JJP takes the issue of addiction very seriously - as mentioned previously we actively monitor this through adverse events reporting and analysis of market data. Moving a product from S3 to S4 will not however, solve the problem of misuse or abuse. There are medicines only available through prescription which are still abused. These include growth hormones and anabolic steroids, opioids and benzodiazepines. Oxycontin and alprazolam are currently the most abused drugs in Australia and the only means by which to obtain them is through a doctor's prescription. This is largely a result of unmonitored of doctor-shopping, and the lack of shared health records in Australia.

There is a significant risk that the desired outcome of reduced misuse will do nothing more that shift the issue from one healthcare domain to another (pharmacy to general practice) or move the issue to different substances e.g. codeine to oxycontin.

In contrast, monitoring of potential misuse has been successfully achieved in the community pharmacy care setting through the pseudoephedrine-monitoring 'Project STOP' program which has greatly reduced the diversion of PSE-containing products into the criminal supply chain in most states.

Conclusions

Rescheduling is a blunt instrument being considered to limit consumer access to the cold and flu treatment category, as a consequence of anecdotal reports of misuse of a combination in another treatment area (analgesia).

JJP is aware of no new evidence emerging since the 2009/10 NDPSC decisions to suggest the population is inappropriately using codeine containing cold and flu products. Evidence provided in this submission clearly supports the notion that the current scheduling of cold and flu products with codeine is appropriate and that the absolute pack sales of codeine-combination analgesic products has decreased dramatically since rescheduling to S3 in 2009.

The current scheduling arrangements for cold and flu products with codeine have remained appropriate. Consumers appear to have a preference or requirement for different levels of treatment to appropriately self-manage their symptoms of cold and flu. This ranges from simple unscheduled treatments available in grocery, to products available as S2 in pharmacy, and then S3 available behind the counter because of the PSE content.

Codeine-containing cold and flu products are 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. Analgesic use is different with some users inappropriately continuing use for the treatment of chronic pain. Due to the differences in the way these different products in different categories are used, their associated risks should be considered independently of each other.

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

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

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

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

Johnson & Johnson Pacific

Appendix 2
JJP submission in the Delegate's Interim decision on Codeine
October 2015

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Johnson & Johnson Pacific

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

Johnson & Johnson Pacific (JJP) 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 JJP 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 Codral 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 JJP 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, JJP, along with a number of other interested parties, including but not limited to ASMI, Sanofi and Emeritus Professor Laurence Mather, 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.

JJP 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, JJP 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. JJP 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.

JJP 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 JJP 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).

JJP 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:

JJP 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.

JJP 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.

JJP would also like to highlight an administrative error made by the TGA. During the initial public submission stage, JJP 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 JJP submission was placed on the TGA website, rather than the redacted version provided on the 7th May 2015. It is acknowledged by JJP 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 JJP 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, JJP 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 Codral®. 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, JJP includes a statement that codeine can be addictive in accordance with New Zealand's Medsafe requirements. JJP 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 JJP in its 7th May 2015 submission, together with the JJP 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 JJP 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, JJP 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.

JJP 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, JJP 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, JJP 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 JJP 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.

JJP 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 JJP); 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 JJP 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 JJP 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.

JJP 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. JJP 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."

JJP 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.

JJP 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.

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

JJP 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

JJP 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, JJP 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.

JJP Response:
JJP 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.

JJP 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 JJP 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.

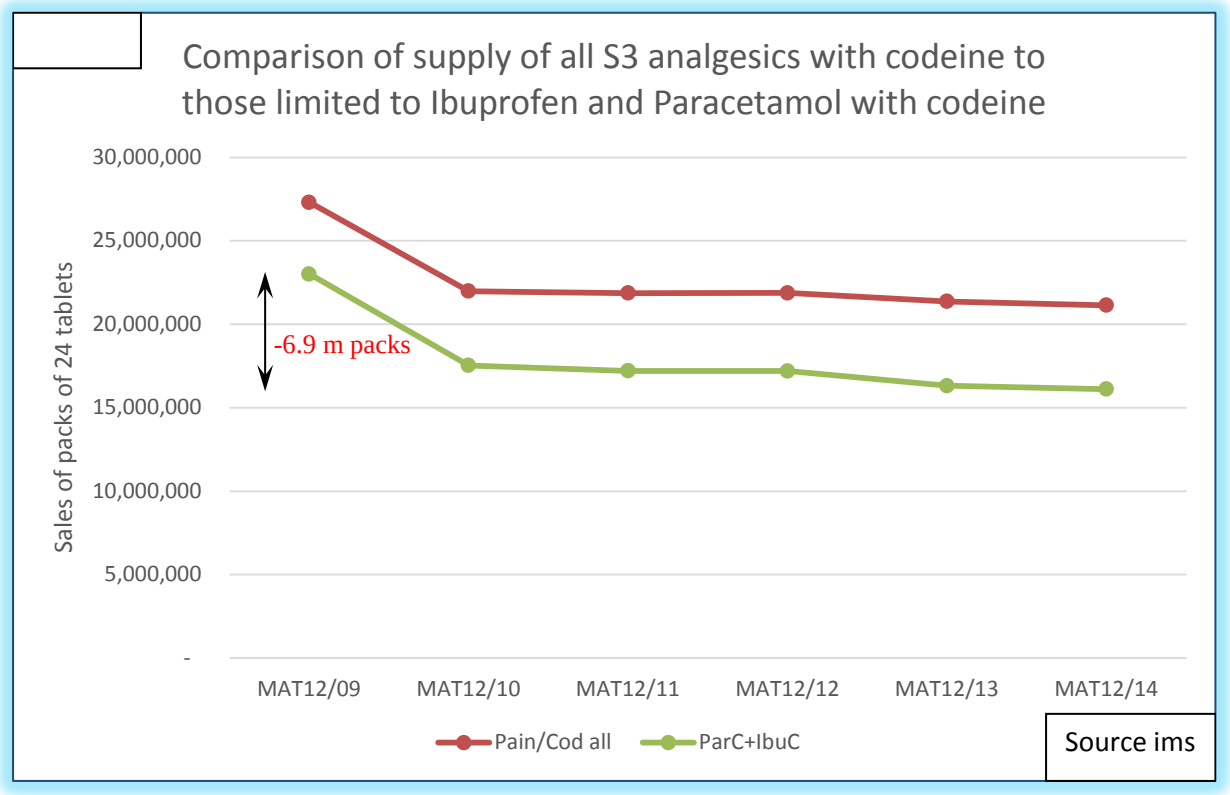
Roxburgh also concludes that *"Codeine-related deaths (with and without other drug toxicity) are increasing as the consumption of codeine-based products increases"*. IMS data clearly demonstrates that since the up scheduling of codeine containing analgesics in 2010, there has been a significant decrease 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.

JJP 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 JJP 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.

JJP 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.

JJP 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.

JJP 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.

JJP Response:
JJP 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.

JJP 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.

JJP 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.

JJP 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.

JJP Response:

This evidence does not relate to codeine containing cold and flu products and therefore is not applicable. Nevertheless JJP 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.

JJP 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.

JJP 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.

JJP 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.

JJP 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.

JJP Response:
This comment does not relate to cold and flu preparations.
JJP 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).

JJP 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.

JJP 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:

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.

JJP 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.

JJP 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.

JJP 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.

JJP Response:

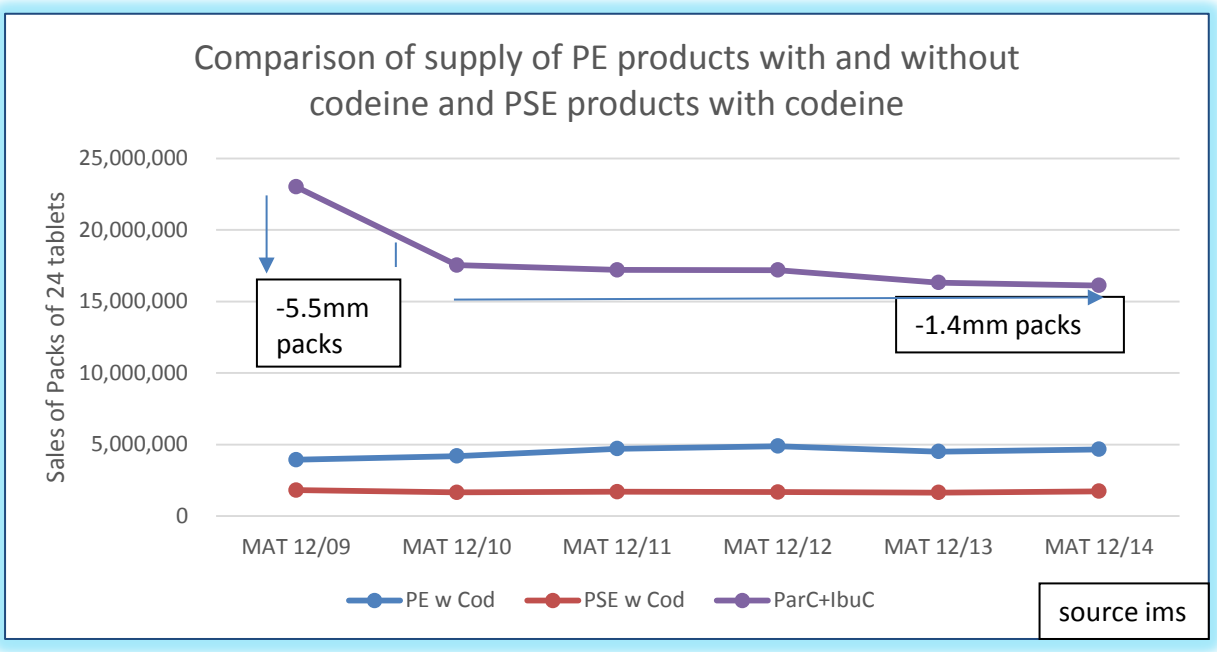
There is no robust evidence to substantiate this comment. This is not relevant for codeine containing cold and flu preparations.

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 JJP 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.

JJP Response:

This is not relevant for codeine containing cold and flu preparations. This comment relates specifically to codeine containing analgesics. JJP 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.

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

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

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

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

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

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

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

JJP 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.

JJP 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.

JJP 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."

JJP 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).

JJP 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.

JJP 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.

JJP Response:
This is not relevant for codeine containing cold and flu preparations. This comment relates specifically to codeine containing analgesics. Nevertheless, JJP believes there is merit in this recommendation for codeine containing analgesics (JJP 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.

JJP 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.

JJP Response:
This is not relevant for codeine containing cold and flu preparations. This comment relates specifically to codeine containing analgesics. However JJP 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.

JJP Response:
This is not relevant for codeine containing cold and flu preparations. This comment relates specifically to codeine containing analgesics. However JJP 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.

JJP 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.

JJP 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.

JJP 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 JJP 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.

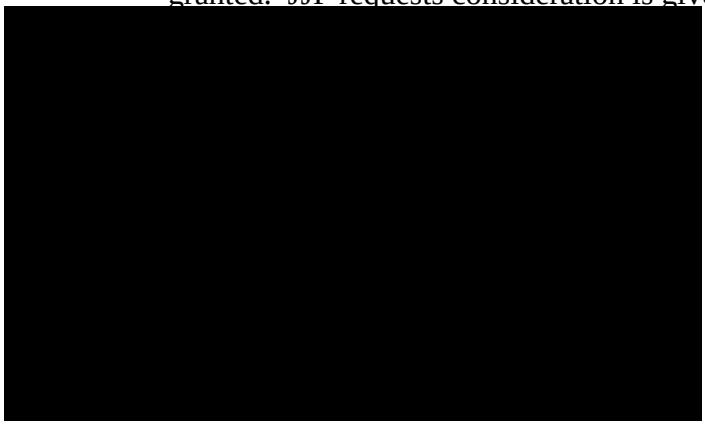
Based on all the available material there is **no evidence** to suggest the risk/benefit profile of codeine containing cold and flu preparations has changed since the NDPSC decision made in 2009 therefore the current schedule 2 entry remains appropriate.

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 JJP 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 JJP to exhaust products already in the supply chain and ensure a smooth transition for retailers and consumers.

Final Position

JJP 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, JJP 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, JJP requests that an appropriate and manageable implementation time is granted. JJP requests consideration is given to a 2 year implementation i.e. November 2017.



Item 6.1 Alcohol Hand Sanitisers

Notwithstanding the issues raised regarding the risk:benefit of ethanol-based hand sanitisers the MCC should consider the risk:benefit of hand sanitisers containing isopropyl alcohol.

On the basis of eye, nose and throat irritation, the American Conference of Governmental Industrial Hygienists (ACGIH) has recommended a threshold limit value of 400 ppm for environmental isopropryl alcohol exposure. [1] If for example a health-care worker applies 90 mL (3 mL × 30 daily hand rubs) of a 70% w/w isopropanol hand rub per shift, a maximum of 67 g will evaporate into the air. If no air exchange takes place in a 12 m^3 room, a maximal isopropanol concentration of 5,500 mg/m^3 in air will result, which is approximately five times above the recommended occupational TWA (980 mg/m^3). [1]

At present, I am unsure if there are any restrictions on the isopropyl alcohol content of General Sale hand sanitisers, or any appropriate warnings regarding exposure.

Reference:

1. Bessonneau V et al., Can Intensive Use of Alcohol-Based Hand Rubs Lead to Passive Alcoholization*? Int. J. Environ. Res. Public Health*. 2010: 7; 3038-3050.

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Review

Can Intensive Use of Alcohol-Based Hand Rubs Lead to Passive Alcoholization?

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Abstract: Hand disinfection with alcohols-based hand rubs (ABHRs) are known to be the most effective measure to prevent nosocomial infections in healthcare. ABHRs contain on average 70% by weight of one or more alcohols. During the hand rubbing procedure, users are exposed to these alcohols not only through dermal contact, but also via inhalation, due to the physical and chemical properties of alcohols volatilizing from alcoholic solutions or gels into the air. Ethanol ingestion is well known to increase risks of several diseases (affecting the pancreas, liver, cardiovascular system…), but there is a lack of knowledge about the effects of exposure to other alcohols (including *n*- or isopropanol) via inhalation and dermal contact, despite the worldwide use of ABHRs. This work aims at discussing possible health effects related to unintentional alcoholization (via inhalation and dermal contact) from professional ABHR usage to suggest the need for more research in this area (but not to question the value of ABHRs). Based upon an average of 30 hand rubbings per healthcare professional per day, it can be assumed that a healthcare worker may be exposed to a maximum 5,500 mg/m^3 per work shift, five times above the recommended occupational time weighted average limit. Thus, in order to answer the question posed in the title, studies on spatial and temporal variability of alcohol emission from ABHRs in real world situations and studies on certain high risk individuals are needed.

Keywords: alcohol-based hand rubs; passive alcoholization; exposure; health-care workers; indoor air

1. Introduction

The effect of hand hygiene interventions on rates of gastrointestinal and respiratory illnesses is well known. Moreover, hand hygiene is the simplest and most effective measure to reduce hospital-acquired infections [1]. During patient care, the risk of hands contamination depends on the type of nursing activity. "Dirty activities" (e.g., washing incontinent patients) are higher risk than "clean activities" (e.g., taking a patient's pulse or oral temperature). For many decades, hygienic hand washing with non-medicated or medicated soap and water were regarded in many countries as the best method to prevent nosocomial infections in healthcare [2]. Since the 1960s and the commercialization of the first alcohol-based liquid cleanser (Sterillium), alcoholic solutions are more and more used for hand disinfection [2,3]. Several *in vitro* and *in vivo* studies have indicated considerably better antimicrobial killing with the use of alcohol-based hand rubs (ABHRs) than standard hand washing with soaps [4-6]. Alcohols are bactericidal, virucidal, myobactericidal and fungicidal [7]. In addition, antiseptic soaps have other significant disadvantages compared to ABHRs, such as skin irritation [8-10], the need for access to a sink with water supply for washing and rinsing [7], or the longer time spent on the hand washing procedure [11]. In the light of these studies, the CDC has published guidelines for hand hygiene in healthcare [12] clearly favoring the use of ABHRs over antimicrobial soaps. Although the frequency of hygienic hand disinfection depends on the nature of activities and the compliance rate within each healthcare service, Voss and Widmer [11] have estimated that on average 20 hand disinfections are carried out per healthcare worker per shift.

It is well documented that chronic alcohol ingestion is correlated with an increased risk of cardiovascular, pancreas or liver diseases, and psychological disorders [13]. Damage to the central nervous system and to the peripheral one can also occur from alcohol misuse. The health effects of alcohol ingestion have led the International Agency for Research on Cancer (IARC) to classify ethanol and alcoholic beverages as Group 1 carcinogens [14].

Contrary to alcohol ingestion, there is limited data regarding inhalation and dermal exposure to alcohol. Given the health effects of alcohol ingestion, it can be assumed that alcohol absorption throughout inhalation and in a lesser extent via dermal contact might induce the same health negative effects in the long term. Kramer *et al.* [15] reported that the quantity of ethanol absorbed after excessive hand disinfection is below toxic levels for humans. In context of the H1N1 flu pandemic, or other coming infectious crisis, several interventions to improve compliance with hands disinfection products have been implemented for healthcare workers and people in hospitals and it can be assumed that before long ABHRs will be used more frequently and by more people. In this work, the possible passive alcoholization risk for healthcare workers caused by the use of ABHRs is discussed without questioning the importance of ABHRs to reduce cross-transmissions. Passive alcoholization refers to the unintentional alcohol intake via inhalation and/or dermal absorption.

2. Alcohol-Based Hands Rubs

The concept of using alcohol for hand antisepsis seems to have appeared in the early 19th century. In the 1890s and early 1900s, the germicidal activity of alcohol was demonstrated and it was proposed for use as a skin disinfectant [16]. The antimicrobial activity is due to alcohol's (ethanol's) ability to denature proteins [17]. Alcohols are effective against most vegetative Gram-positive and Gram-negative bacteria, many fungi, especially *Mycobacterium tubercolisis*, and a variety of enveloped (e.g., hepatitis B, human immunodeficiency virus and herpes simplex virus) and non-enveloped (e.g., enterovirus, adenovirus and rotavirus) viruses [18,19]. Most ABHRs contain one or more alcohols including ethanol, *n*-propanol and isopropanol. Table 1 provides physical and chemical characteristics of alcohols used in ABHR formulation [20-25].

Table 1. Physical and chemical properties of alcohols used in ABHR formulation.

Compounds	Molecular weight (g/mol)	Structural formula	Water solubility at 25 °C (mg/L)	Henry's constant at 25 °C ($atm.m^3/mol$)
Ethanol	46.07	CH_3-CH_2OH	Fully miscible	5×10^{-6}
n-Propanol	60.1	CH_3-CH_2-CH_2OH	Fully miscible	7.41×10^{-6}
Isopropanol	60.1	CH_3-CH_2OH-CH_3	Fully miscible	8.10×10^{-6}
Aminomethylpropanol	89.14	CH_3-$C(CH_3)(NH_2)$-CH_2OH	Fully miscible	6.48×10^{-10}
Benzyl alcohol	108.14	Ph-CH_2OH	42.9	3.37×10^{-7}
Phenoxyethanol	138.17	Ph-O-CH_2-CH_2OH	26,700	4.72×10^{-8}

Ethanol, *n*-propanol and isopropanol are the most volatile compounds, as proven by their Henry's constant. Henry's constant represents the solubility of a chemical compound in a liquid at a particular temperature. This constant reflects the relative volatility of a chemical compound. Some 54% of commercially available alcohol products are made up by two different alcohols (Figure 1), and ethanol and isopropanol are the most used components (Table 2).

Figure 1. Breakdown of the different ABHR formulations. Data from SFHH [26].

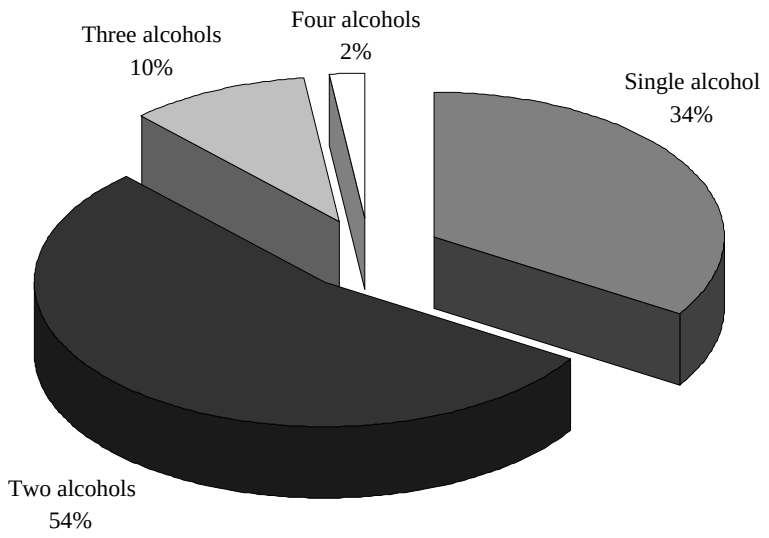


Table 2. Distribution of alcohols, in percentage (%), among different formulations: single (1), two (2), three (3), and four (4) alcohol-based hand rubs. Data from SFHH [26].

Compounds	1	2	3	4	Total
Ethanol	25%	46%	29%	25%	39%
n-Propanol	6%	9%	0%	25%	8%
Isopropanol	71%	39%	21%	25%	40%
Aminomethylpropanol	0%	0%	14%	0%	2%
Benzyl alcohol	0%	0%	7%	0%	1%
Phenoxyethanol	0%	6%	29%	25%	9%

Ethanol is used almost equally in the formulation of the four categories of ABHRs, depending on the number of alcohols (one, two, three or four). Isopropanol is mainly used in the single alcohol category. Other active ingredients, such as chlorhexidine or triclosan may be added to ensure a residual antimicrobial activity [19,26]. Besides ABHRs, alcohol-free hand hygiene products containing benzalkonium chloride or chlorhexidine have been proposed [19]. A few studies have reported that these products are less effective in preventing cross-transmission of pathogens [1,3,27]. Since the 2000s, several studies have emphasized the importance of high compliance with ABHR usage as a hand hygiene program to reduce nosocomial infections [2,28-30]. Scheithauer *et al.* [31] have observed a regular 78% increase of ABHR usage in intensive care units between 2003 and 2008. A recent review has found an overall median compliance rate with hand hygiene guidelines in hospital care of 40% [32].

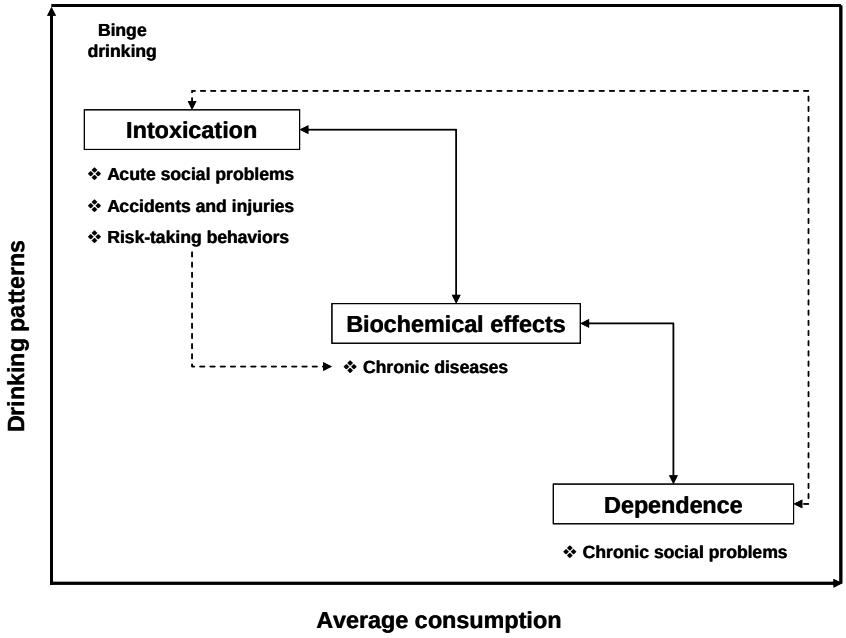
3. Intentional Alcohol Intake

Intentional alcohol intake defines the consumption of alcoholic beverages, used in many societies for many purposes. Alcohol consumption is related to a wide range of physical, mental and social harms. As shown in Figure 2, the link between alcohol consumption and health consequences depends on the average volume of consumption, drinking patterns, and on the mediating mechanisms: intoxication, dependence, and biochemical effects [33]. Alcohols-related harms are mediated by three mechanisms: intoxication, dependence and biochemical effects.

Intoxication is an acute disease listed in the 10th revision of the International Classification of Diseases and Related Health Problems (ICD-10), and occurring after ingestion of a large amount of alcoholic beverages in a limited period of time [34]. Most of the symptoms of alcohol intoxication are due to the effects of alcohol on the central nervous system.

Alcohol dependence has been classified in the 9th revision of the International Classification of Diseases and Related Health Problems (ICD-9) as a mental disorder. The action of alcohol on the brain induces complex changes in brain chemistry and lead to neuroadaptation, increasing alcohol tolerance [35,36].

Figure 2. Overview of alcohol-related harmful mechanisms (adapted from Rehm *et al.* [33]).



The biochemical effects of alcohol seem to influence chronic disease in harmful ways [33]. Increased rates of heart attacks, hypertension and other cardiovascular diseases are well associated with heavy drinking episodes [37-39]. Alcohol is a potent teratogen and high consumption of alcoholic beverages during pregnancy leads to fetal alcohol syndrome (FAS), characterized by growth deficiencies, craniofacial abnormalities, prematurity and serious neurobiological dysfunctions, including mental retardation [40,41]. Repeated alcohol consumption has been estimated as the major cause of liver cirrhosis [42]. Long term alcohol misuse during adolescence impairs brain development and increases neuropsychatric and cognitive disorders [43,44]. Chronic consumption can also cause thiamine deficiency inducing neurological disorder known as Wernicke-Korsakoff Syndrome (WKS) [45,46]. WKS is a combination of Wernicke's encephalopathy (WE) and Korsakoff's psychosis and the main symptoms include mental confusion, oculomotor disturbances, behavioral abnormalities and memory impairments [45,47]. The International Agency for Research on Cancer (IARC) has classified alcohol drinking as carcinogenic to humans [14]. Alcohol is recognized as a risk factor of several cancers: mouth (lip and tongue), pharynx, larynx, hypopharynx, esophagus, liver, breast, stomach, pancreas, colon, rectum, prostate, salivary glands, ovarium, endometrium and bladder [14,48-53]. Finally, cancer risks appear to increase with increasing volume of alcohol consumed [50]. The main chronic diseases related to alcohol drinking are reported in Table 3.

Table 3. Summary of the main chronic diseases link to alcohol consumption.

Main chronic diseases	References (selection)
Liver cirrhosis	[42]
Fetal Alcohol Syndrome (FAS)	[40,41]
Cancer	[14,48-53]
Cardiovascular disorders	[37-39]
Neurological disorders	[43-47]

4. Unintentional Alcohol Intake

Alcohols, as chemical substances, are widely used as solvents in the paint, adhesive, varnish, ink, cosmetic and perfume industry, and as disinfectants in cleaning products. Few studies have focused on occupational exposure to alcohols [54-57]. Brugnone *et al.* [54] have sampled isopropanol in air, breath, blood and urine to assess the occupational exposure of 12 workers in a print works. The authors reported an isopropanol concentration range between 7 and 645 mg/m^3 in air samples, and between 4 and 437 mg/m^3 in breath samples, but with no detection in urine and blood. They have also observed a significant correlation between environmental and exhaled air concentrations.

During the 1950s and 1960s; floor layers used to handle between 20 and 30 L per day of alcohol-based glues [55,56]. In the early 1970s, an exposure assessment measured ethanol or methanol levels around 500 mg/m^3 [57]. Since the 1970s, efforts have been made to reduce exposure of floor layers to organic solvents, and alcohol-based glues have been substituted by water-based glues or solvents with low volatility and new types of glues have been designed. In addition, since the 1980s, floor layers typically wear protective masks containing charcoal filters [56].

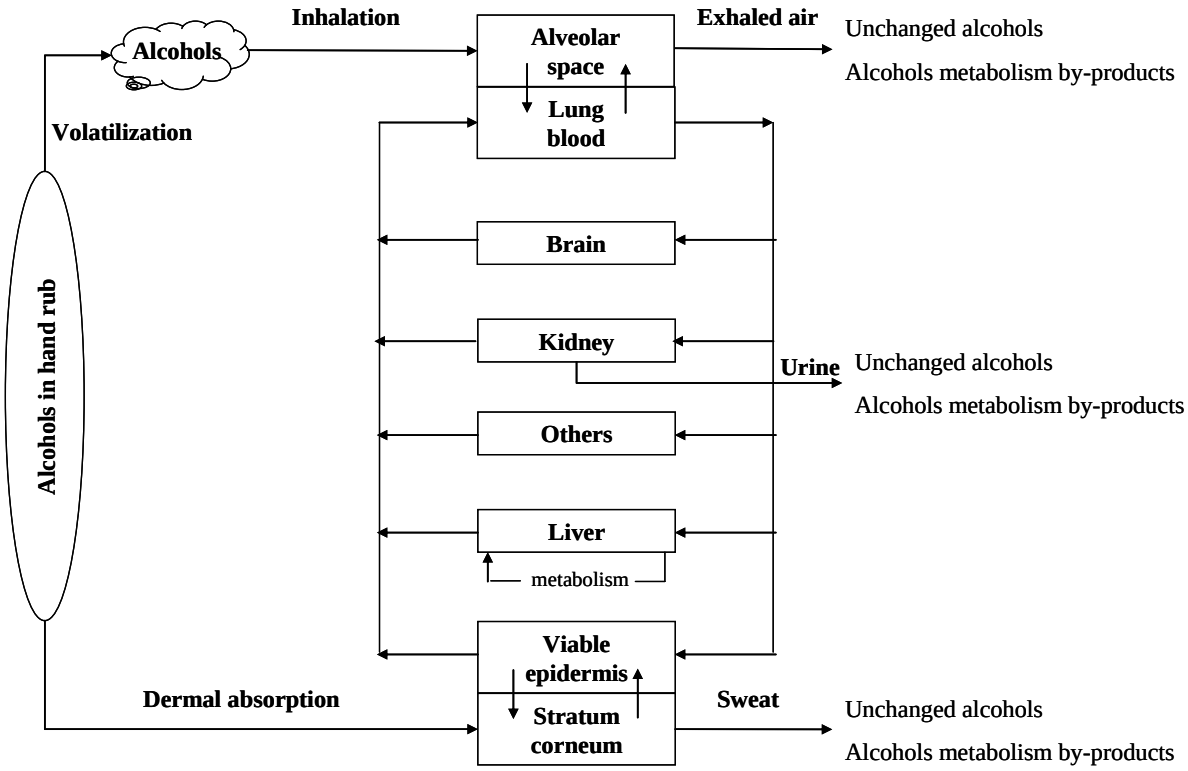
Cumulative occupational and home exposures to well-known irritants, such as isopropyl alcohol, can cause respiratory system irritations. Tonini *et al.* [58] have reported a case of vocal cord dysfunction, diagnosed in a nurse in charge of cleaning endoscopy instruments. As consequence, reprocessing of instruments in washer disinfectors is strongly recommended.

Some healthcare workers have complained of an unpleasant smell associated with the use of alcohol-based products use like ABHRs [1]. During hand rubbing, users are exposed to different types of alcohols (e.g., ethanol, *n*-propanol and isopropanol) via inhalation and dermal contact. Depending on manufacturer's recommendations, a good hand disinfection procedure is generally achieved with a 30 second hand rubbing with 3 mL of alcohol-based products. Some manufacturers recommend doing this procedure twice [26]. Under practical conditions, this procedure averages between 6 to 24 seconds [30].

The CDC hands hygiene guidelines have reported that an average of five hand rubs per shift to as many as 30 hand rubs per shift are carried out per health care worker [12]. However, this number varies markedly, depending on the nature of the clinical activity, the hospital setting, or the healthcare worker's adherence with hands hygiene programs [30]. Indeed, the CDC hands hygiene guidelines has reported that adherence of healthcare workers with hygiene practices varies widely between 5% and 81%, with an overall average of 40% [12]. The SUMER survey conducted in 2003, has reported that healthcare workers are six times more exposed to alcohols (35% *versus* 7%) than other workers [59].

ABHR users are exposed to alcohols via inhalation and dermal route. Alcohols are volatile organic oxygenated species, water soluble, and highly mobile. A schematic diagram of alcohol absorption, distribution, metabolization and excretion pathways is shown in Figure 3. Through inhalation exposure, alcohols are readily absorbed into the body via the lungs. In the alveoli, a gas-blood equilibrium is rapidly established by passive diffusion of alcohol vapors between alveolar gas and blood. To a lesser extent, alcohols are also absorbed through dermal contact, except ethanol for which percutaneous absorption is very low (about 1%) [24].

Figure 3. Alcohol absorption, distribution, metabolization, and excretion pathways.



5. Risk Assessment

Absorbed alcohols are widely diffused throughout the organism due to their high water solubility and are rapidly distributed into highly vascular organs such as brain and liver. Alcohols are eliminated from the body mainly by metabolism. A small amount is excreted in unmetabolized form in urine, sweat and breath (2%–5%) [23,24].

Alcohols are metabolized in the liver via two different pathways: the alcohol dehydrogenase (ADH) pathway located in the cytosol of hepatocytes, and the microsomal ethanol-oxidizing system (MEOS; CYP2E1) pathway located on the endoplasmic reticulum [60]. Through both pathways ethanol, *n*-propanol and isopropanol are metabolized to acetaldehyde, propionaldehyde and acetone, respectively [22,61]. A part of the by-products formed are then eliminated from the organism via the kidneys and by exhaled air. Another part is converted to acetate and propionate by aldehyde dehydrogenase (ALDH) located in the mitochondria. The acetate and propionate produced are released into the blood and are oxidized by peripheral tissues to acetic and propionic acid and finally into carbon dioxide and water [62-65].

Alcohols have low acute toxicity by all routes of exposure. The critical effect is the irritation of respiratory system, eyes, and mucous membranes. Higher concentrations may cause central nervous system effects including dizziness, nausea, hypotension, and hypothermia. Through inhalation and dermal contact, IARC has classified isopropanol in Group 3 (inadequate evidence for carcinogenicity to humans), whereas *n*-propanol and ethanol are not evaluated as chemical substances.

On the basis of eye, nose and throat irritation, the American Conference of Governmental Industrial Hygienists (ACGIH) has recommended a threshold limit value of 1,000 ppm, 200 ppm and 400 ppm

for ethanol, *n*-propanol and isopropanol, respectively, in air over an 8-hours exposure [or time-weighted average limit (TWA)], as summarized in Table 4.

Table 4. Recommended alcohol occupational exposure limit values.

Compounds	Country	8-hour time-weighted average (TWA)		15 min short-term exposure level (STEL)	
		ppm	mg/m^3	ppm	mg/m^3
Ethanol	France	1,000	1,950	5,000	9,500
	United States	1,000	1,950	ND	ND
n-Propanol	France	200	500	ND	ND
	United States	200	500	250	625
Isopropanol	France	400	980	ND	ND
	United States	400	980	500	1,225

ND: no data; TWA: time-weighted average; STEL: short-term exposure limit.

For *n*-propanol and isopropanol, 15 min short-term exposure levels (STEL) of 250 ppm and 500 ppm have been added, respectively. In France, the same TWA limits for ethanol, *n*-propanol and isopropanol have been recommended, and a 15 min STEL of 5,000 ppm for ethanol has been proposed. Whereas acute and chronic health effects resulting from alcoholic beverage consumption are well known, there is a lack of knowledge regarding exposure via the inhalation and dermal routes. Despite intensive use of ABHRs in health-care, and peoples' growing interest in these products, only a few studies have addressed the issue of alcohol intake during hand rubbing procedures [15,66]. Kramer *et al.* [15] assessed the ethanol absorption level during hand hygiene and surgical disinfection procedures. They have tested three ABHRs containing 95 % and 85 % w/w ethanol, and 55% w/w ethanol with 10% w/w *n*-propanol. The authors reported that the total amount of alcohol absorbed ranged from 358 to 1,365 mg and from 477 to 1,542 mg, respectively, after 20 hygienic and 10 surgical hand disinfections. Miller *et al.* [66] have also investigated blood ethanol concentrations before and after 50 applications of 5 mL of 62 % ethanol products in five volunteers. They have observed a blood ethanol level lower than 50 mg/L in all five participants. Both studies have concluded that ethanol absorption is below the toxic levels for humans.

These studies on blood ethanol concentrations resulting from intensive hand rub applications over a limited period of time [15-66] have in common one major limitation, the use of only ethanol-based hand rubs, whereas, as described in Section 2, most sanitizers used nowadays are made up of at least two different alcohols, typically ethanol and isopropanol, the latter producing irritation of the respiratory system and damage to the central nervous system, and being classified in Group 3 by IARC [62-64].

Finally, a simple theoretical mass balance calculation of isopropanol during hand rubbing can be considered, as proposed by Kramer *et al.* [15] (this could be extended to other alcohols). If for example a health-care worker applies 90 mL (3 mL × 30 daily hand rubs) of a 70% w/w isopropanol hand rub per shift, a maximum of 67 g will evaporate into the air. If no air exchange takes place in a 12 m^3 room, a maximal isopropanol concentration of 5,500 mg/m^3 in air will result, which is approximately five times above the recommended occupational TWA (980 mg/m^3). This calculation is the worst case based on lack of air movement. Nowadays, hospital facilities have air movement from

heaters and air conditioners blowing air. However, this result shows that there is a need to characterize indoor air contamination close to users, assessing spatial and temporal variability of alcohols in air. Evaporation of alcohols during hand disinfection is a localized discontinuous source of pollution and may lead to a continuous and diffuse background contamination in intensive rubbing rooms, so ABHR users might be exposed during hand rubbing to passive alcoholization.

6. Conclusions

Ingestion of alcohol (ethanol) is well known to cause adverse health effects such as liver cirrhosis, fetal alcohol syndrome and cancer, but there is no evidence to suggest intoxication or dependence could occur with use of ABHRs. The only issue of passive alcoholization would relate to its biochemical effects. In addition, the use of ABHRs in healthcare settings as part of a hand hygiene program has a definable, clear-cut value, while the questions being raised in this article are preliminary and the answers are far from being settled.

In a context of an increased use of ABHRs, the issue of exposure to alcohols mainly via inhalation but also through dermal absorption should be considered to determine how safe air is. Despite the existence of a few studies, there is a general lack of knowledge about alcohol, especially *n*-propanol and isopropanol, contamination levels in the environment of ABHR users such as health care workers. Thus, more research is needed for contamination assessment, including spatial and temporal variability of alcohol emissions from ABHRs to indoor air (peak *vs* average concentrations) in real world situations. In addition, the sampling and analysis of alcohols and related metabolized by-products in exhaled air of non-drinkers might be used as an exposure biomarker, as a complement to serum alcohol levels. The next layer of studies could be performed on individuals with known liver disease to see if their ability to detoxify minute amounts of alcohol would put that at special risk. These data could improve our knowledge about exposure to alcohols through the inhalation route linked to the frequent use of ABHRs, in order to be able to propose recommendations such as increases in the air exchange rate within healthcare settings, if needed.

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55th MCC Agenda

6.1 Further in support of the submission we provide the attached 210 review from France that concluded:

> "Based upon an average of 30 hand rubbings per healthcare professional per day, it can be assumed that a healthcare worker may be exposed to a maximum 5,500 mg/m^3 per work shift, five times above the recommended occupational time weighted average limit."

Thus, a child need only receive approximately one (1) alcohol hand sanitiser rub to be exposed to the recommended maximum environmental time weighted average limit.

Alcohol based hand sanitisers for children are a form of passive alcoholisation.

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Review

Can Intensive Use of Alcohol-Based Hand Rubs Lead to Passive Alcoholization?

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Abstract: Hand disinfection with alcohols-based hand rubs (ABHRs) are known to be the most effective measure to prevent nosocomial infections in healthcare. ABHRs contain on average 70% by weight of one or more alcohols. During the hand rubbing procedure, users are exposed to these alcohols not only through dermal contact, but also via inhalation, due to the physical and chemical properties of alcohols volatilizing from alcoholic solutions or gels into the air. Ethanol ingestion is well known to increase risks of several diseases (affecting the pancreas, liver, cardiovascular system…), but there is a lack of knowledge about the effects of exposure to other alcohols (including *n*- or isopropanol) via inhalation and dermal contact, despite the worldwide use of ABHRs. This work aims at discussing possible health effects related to unintentional alcoholization (via inhalation and dermal contact) from professional ABHR usage to suggest the need for more research in this area (but not to question the value of ABHRs). Based upon an average of 30 hand rubbings per healthcare professional per day, it can be assumed that a healthcare worker may be exposed to a maximum 5,500 mg/m^3 per work shift, five times above the recommended occupational time weighted average limit. Thus, in order to answer the question posed in the title, studies on spatial and temporal variability of alcohol emission from ABHRs in real world situations and studies on certain high risk individuals are needed.

Keywords: alcohol-based hand rubs; passive alcoholization; exposure; health-care workers; indoor air

1. Introduction

The effect of hand hygiene interventions on rates of gastrointestinal and respiratory illnesses is well known. Moreover, hand hygiene is the simplest and most effective measure to reduce hospital-acquired infections [1]. During patient care, the risk of hands contamination depends on the type of nursing activity. "Dirty activities" (e.g., washing incontinent patients) are higher risk than "clean activities" (e.g., taking a patient's pulse or oral temperature). For many decades, hygienic hand washing with non-medicated or medicated soap and water were regarded in many countries as the best method to prevent nosocomial infections in healthcare [2]. Since the 1960s and the commercialization of the first alcohol-based liquid cleanser (Sterillium), alcoholic solutions are more and more used for hand disinfection [2,3]. Several *in vitro* and *in vivo* studies have indicated considerably better antimicrobial killing with the use of alcohol-based hand rubs (ABHRs) than standard hand washing with soaps [4-6]. Alcohols are bactericidal, virucidal, myobactericidal and fungicidal [7]. In addition, antiseptic soaps have other significant disadvantages compared to ABHRs, such as skin irritation [8-10], the need for access to a sink with water supply for washing and rinsing [7], or the longer time spent on the hand washing procedure [11]. In the light of these studies, the CDC has published guidelines for hand hygiene in healthcare [12] clearly favoring the use of ABHRs over antimicrobial soaps. Although the frequency of hygienic hand disinfection depends on the nature of activities and the compliance rate within each healthcare service, Voss and Widmer [11] have estimated that on average 20 hand disinfections are carried out per healthcare worker per shift.

It is well documented that chronic alcohol ingestion is correlated with an increased risk of cardiovascular, pancreas or liver diseases, and psychological disorders [13]. Damage to the central nervous system and to the peripheral one can also occur from alcohol misuse. The health effects of alcohol ingestion have led the International Agency for Research on Cancer (IARC) to classify ethanol and alcoholic beverages as Group 1 carcinogens [14].

Contrary to alcohol ingestion, there is limited data regarding inhalation and dermal exposure to alcohol. Given the health effects of alcohol ingestion, it can be assumed that alcohol absorption throughout inhalation and in a lesser extent via dermal contact might induce the same health negative effects in the long term. Kramer *et al.* [15] reported that the quantity of ethanol absorbed after excessive hand disinfection is below toxic levels for humans. In context of the H1N1 flu pandemic, or other coming infectious crisis, several interventions to improve compliance with hands disinfection products have been implemented for healthcare workers and people in hospitals and it can be assumed that before long ABHRs will be used more frequently and by more people. In this work, the possible passive alcoholization risk for healthcare workers caused by the use of ABHRs is discussed without questioning the importance of ABHRs to reduce cross-transmissions. Passive alcoholization refers to the unintentional alcohol intake via inhalation and/or dermal absorption.

2. Alcohol-Based Hands Rubs

The concept of using alcohol for hand antisepsis seems to have appeared in the early 19th century. In the 1890s and early 1900s, the germicidal activity of alcohol was demonstrated and it was proposed for use as a skin disinfectant [16]. The antimicrobial activity is due to alcohol's (ethanol's) ability to denature proteins [17]. Alcohols are effective against most vegetative Gram-positive and Gram-negative bacteria, many fungi, especially *Mycobacterium tubercolisis*, and a variety of enveloped (e.g., hepatitis B, human immunodeficiency virus and herpes simplex virus) and non-enveloped (e.g., enterovirus, adenovirus and rotavirus) viruses [18,19]. Most ABHRs contain one or more alcohols including ethanol, *n*-propanol and isopropanol. Table 1 provides physical and chemical characteristics of alcohols used in ABHR formulation [20-25].

Table 1. Physical and chemical properties of alcohols used in ABHR formulation.

Compounds	Molecular weight (g/mol)	Structural formula	Water solubility at 25 °C (mg/L)	Henry's constant at 25 °C ($atm.m^3/mol$)
Ethanol	46.07	CH_3-CH_2OH	Fully miscible	5×10^{-6}
n-Propanol	60.1	CH_3-CH_2-CH_2OH	Fully miscible	7.41×10^{-6}
Isopropanol	60.1	CH_3-CH_2OH-CH_3	Fully miscible	8.10×10^{-6}
Aminomethylpropanol	89.14	CH_3-$C(CH_3)(NH_2)$-CH_2OH	Fully miscible	6.48×10^{-10}
Benzyl alcohol	108.14	Ph-CH_2OH	42.9	3.37×10^{-7}
Phenoxyethanol	138.17	Ph-O-CH_2-CH_2OH	26,700	4.72×10^{-8}

Ethanol, *n*-propanol and isopropanol are the most volatile compounds, as proven by their Henry's constant. Henry's constant represents the solubility of a chemical compound in a liquid at a particular temperature. This constant reflects the relative volatility of a chemical compound. Some 54% of commercially available alcohol products are made up by two different alcohols (Figure 1), and ethanol and isopropanol are the most used components (Table 2).

Figure 1. Breakdown of the different ABHR formulations. Data from SFHH [26].

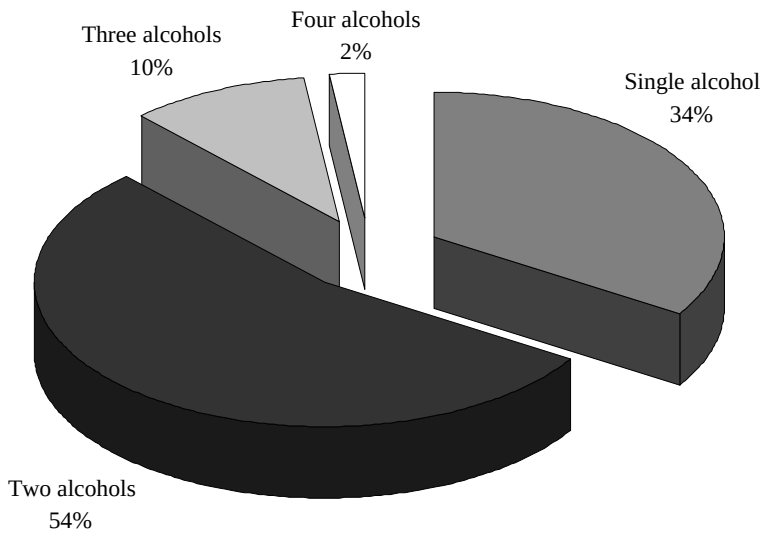


Table 2. Distribution of alcohols, in percentage (%), among different formulations: single (1), two (2), three (3), and four (4) alcohol-based hand rubs. Data from SFHH [26].

Compounds	1	2	3	4	Total
Ethanol	25%	46%	29%	25%	39%
n-Propanol	6%	9%	0%	25%	8%
Isopropanol	71%	39%	21%	25%	40%
Aminomethylpropanol	0%	0%	14%	0%	2%
Benzyl alcohol	0%	0%	7%	0%	1%
Phenoxyethanol	0%	6%	29%	25%	9%

Ethanol is used almost equally in the formulation of the four categories of ABHRs, depending on the number of alcohols (one, two, three or four). Isopropanol is mainly used in the single alcohol category. Other active ingredients, such as chlorhexidine or triclosan may be added to ensure a residual antimicrobial activity [19,26]. Besides ABHRs, alcohol-free hand hygiene products containing benzalkonium chloride or chlorhexidine have been proposed [19]. A few studies have reported that these products are less effective in preventing cross-transmission of pathogens [1,3,27]. Since the 2000s, several studies have emphasized the importance of high compliance with ABHR usage as a hand hygiene program to reduce nosocomial infections [2,28-30]. Scheithauer *et al.* [31] have observed a regular 78% increase of ABHR usage in intensive care units between 2003 and 2008. A recent review has found an overall median compliance rate with hand hygiene guidelines in hospital care of 40% [32].

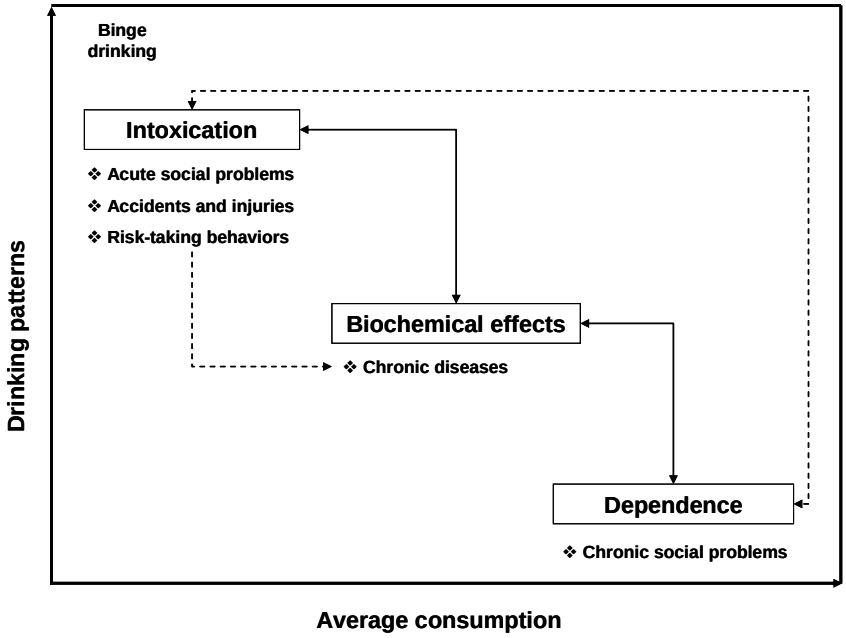
3. Intentional Alcohol Intake

Intentional alcohol intake defines the consumption of alcoholic beverages, used in many societies for many purposes. Alcohol consumption is related to a wide range of physical, mental and social harms. As shown in Figure 2, the link between alcohol consumption and health consequences depends on the average volume of consumption, drinking patterns, and on the mediating mechanisms: intoxication, dependence, and biochemical effects [33]. Alcohols-related harms are mediated by three mechanisms: intoxication, dependence and biochemical effects.

Intoxication is an acute disease listed in the 10th revision of the International Classification of Diseases and Related Health Problems (ICD-10), and occurring after ingestion of a large amount of alcoholic beverages in a limited period of time [34]. Most of the symptoms of alcohol intoxication are due to the effects of alcohol on the central nervous system.

Alcohol dependence has been classified in the 9th revision of the International Classification of Diseases and Related Health Problems (ICD-9) as a mental disorder. The action of alcohol on the brain induces complex changes in brain chemistry and lead to neuroadaptation, increasing alcohol tolerance [35,36].

Figure 2. Overview of alcohol-related harmful mechanisms (adapted from Rehm *et al.* [33]).



The biochemical effects of alcohol seem to influence chronic disease in harmful ways [33]. Increased rates of heart attacks, hypertension and other cardiovascular diseases are well associated with heavy drinking episodes [37-39]. Alcohol is a potent teratogen and high consumption of alcoholic beverages during pregnancy leads to fetal alcohol syndrome (FAS), characterized by growth deficiencies, craniofacial abnormalities, prematurity and serious neurobiological dysfunctions, including mental retardation [40,41]. Repeated alcohol consumption has been estimated as the major cause of liver cirrhosis [42]. Long term alcohol misuse during adolescence impairs brain development and increases neuropsychatric and cognitive disorders [43,44]. Chronic consumption can also cause thiamine deficiency inducing neurological disorder known as Wernicke-Korsakoff Syndrome (WKS) [45,46]. WKS is a combination of Wernicke's encephalopathy (WE) and Korsakoff's psychosis and the main symptoms include mental confusion, oculomotor disturbances, behavioral abnormalities and memory impairments [45,47]. The International Agency for Research on Cancer (IARC) has classified alcohol drinking as carcinogenic to humans [14]. Alcohol is recognized as a risk factor of several cancers: mouth (lip and tongue), pharynx, larynx, hypopharynx, esophagus, liver, breast, stomach, pancreas, colon, rectum, prostate, salivary glands, ovarium, endometrium and bladder [14,48-53]. Finally, cancer risks appear to increase with increasing volume of alcohol consumed [50]. The main chronic diseases related to alcohol drinking are reported in Table 3.

Table 3. Summary of the main chronic diseases link to alcohol consumption.

Main chronic diseases	References (selection)
Liver cirrhosis	[42]
Fetal Alcohol Syndrome (FAS)	[40,41]
Cancer	[14,48-53]
Cardiovascular disorders	[37-39]
Neurological disorders	[43-47]

4. Unintentional Alcohol Intake

Alcohols, as chemical substances, are widely used as solvents in the paint, adhesive, varnish, ink, cosmetic and perfume industry, and as disinfectants in cleaning products. Few studies have focused on occupational exposure to alcohols [54-57]. Brugnone *et al.* [54] have sampled isopropanol in air, breath, blood and urine to assess the occupational exposure of 12 workers in a print works. The authors reported an isopropanol concentration range between 7 and 645 mg/m^3 in air samples, and between 4 and 437 mg/m^3 in breath samples, but with no detection in urine and blood. They have also observed a significant correlation between environmental and exhaled air concentrations.

During the 1950s and 1960s; floor layers used to handle between 20 and 30 L per day of alcohol-based glues [55,56]. In the early 1970s, an exposure assessment measured ethanol or methanol levels around 500 mg/m^3 [57]. Since the 1970s, efforts have been made to reduce exposure of floor layers to organic solvents, and alcohol-based glues have been substituted by water-based glues or solvents with low volatility and new types of glues have been designed. In addition, since the 1980s, floor layers typically wear protective masks containing charcoal filters [56].

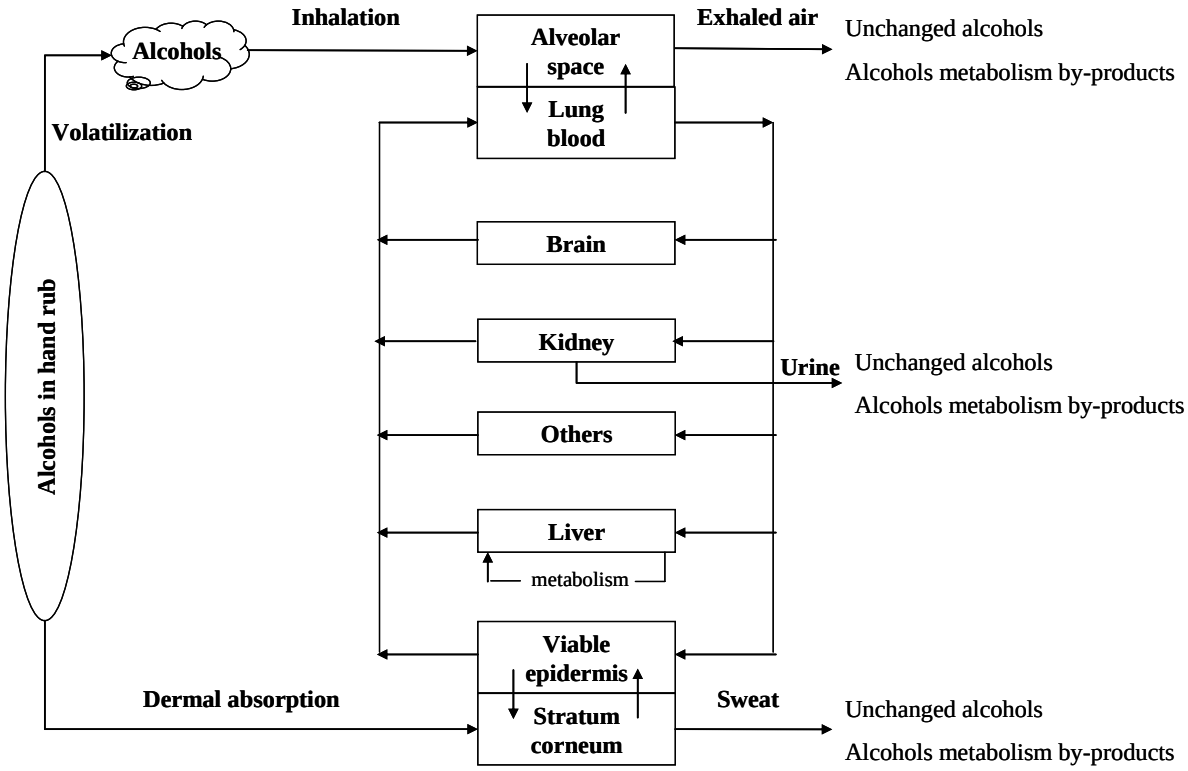
Cumulative occupational and home exposures to well-known irritants, such as isopropyl alcohol, can cause respiratory system irritations. Tonini *et al.* [58] have reported a case of vocal cord dysfunction, diagnosed in a nurse in charge of cleaning endoscopy instruments. As consequence, reprocessing of instruments in washer disinfectors is strongly recommended.

Some healthcare workers have complained of an unpleasant smell associated with the use of alcohol-based products use like ABHRs [1]. During hand rubbing, users are exposed to different types of alcohols (e.g., ethanol, *n*-propanol and isopropanol) via inhalation and dermal contact. Depending on manufacturer's recommendations, a good hand disinfection procedure is generally achieved with a 30 second hand rubbing with 3 mL of alcohol-based products. Some manufacturers recommend doing this procedure twice [26]. Under practical conditions, this procedure averages between 6 to 24 seconds [30].

The CDC hands hygiene guidelines have reported that an average of five hand rubs per shift to as many as 30 hand rubs per shift are carried out per health care worker [12]. However, this number varies markedly, depending on the nature of the clinical activity, the hospital setting, or the healthcare worker's adherence with hands hygiene programs [30]. Indeed, the CDC hands hygiene guidelines has reported that adherence of healthcare workers with hygiene practices varies widely between 5% and 81%, with an overall average of 40% [12]. The SUMER survey conducted in 2003, has reported that healthcare workers are six times more exposed to alcohols (35% *versus* 7%) than other workers [59].

ABHR users are exposed to alcohols via inhalation and dermal route. Alcohols are volatile organic oxygenated species, water soluble, and highly mobile. A schematic diagram of alcohol absorption, distribution, metabolization and excretion pathways is shown in Figure 3. Through inhalation exposure, alcohols are readily absorbed into the body via the lungs. In the alveoli, a gas-blood equilibrium is rapidly established by passive diffusion of alcohol vapors between alveolar gas and blood. To a lesser extent, alcohols are also absorbed through dermal contact, except ethanol for which percutaneous absorption is very low (about 1%) [24].

Figure 3. Alcohol absorption, distribution, metabolization, and excretion pathways.



5. Risk Assessment

Absorbed alcohols are widely diffused throughout the organism due to their high water solubility and are rapidly distributed into highly vascular organs such as brain and liver. Alcohols are eliminated from the body mainly by metabolism. A small amount is excreted in unmetabolized form in urine, sweat and breath (2%–5%) [23,24].

Alcohols are metabolized in the liver via two different pathways: the alcohol dehydrogenase (ADH) pathway located in the cytosol of hepatocytes, and the microsomal ethanol-oxidizing system (MEOS; CYP2E1) pathway located on the endoplasmic reticulum [60]. Through both pathways ethanol, *n*-propanol and isopropanol are metabolized to acetaldehyde, propionaldehyde and acetone, respectively [22,61]. A part of the by-products formed are then eliminated from the organism via the kidneys and by exhaled air. Another part is converted to acetate and propionate by aldehyde dehydrogenase (ALDH) located in the mitochondria. The acetate and propionate produced are released into the blood and are oxidized by peripheral tissues to acetic and propionic acid and finally into carbon dioxide and water [62-65].

Alcohols have low acute toxicity by all routes of exposure. The critical effect is the irritation of respiratory system, eyes, and mucous membranes. Higher concentrations may cause central nervous system effects including dizziness, nausea, hypotension, and hypothermia. Through inhalation and dermal contact, IARC has classified isopropanol in Group 3 (inadequate evidence for carcinogenicity to humans), whereas *n*-propanol and ethanol are not evaluated as chemical substances.

On the basis of eye, nose and throat irritation, the American Conference of Governmental Industrial Hygienists (ACGIH) has recommended a threshold limit value of 1,000 ppm, 200 ppm and 400 ppm

for ethanol, *n*-propanol and isopropanol, respectively, in air over an 8-hours exposure [or time-weighted average limit (TWA)], as summarized in Table 4.

Table 4. Recommended alcohol occupational exposure limit values.

Compounds	Country	8-hour time-weighted average (TWA)		15 min short-term exposure level (STEL)	
		ppm	mg/m^3	ppm	mg/m^3
Ethanol	France	1,000	1,950	5,000	9,500
	United States	1,000	1,950	ND	ND
n-Propanol	France	200	500	ND	ND
	United States	200	500	250	625
Isopropanol	France	400	980	ND	ND
	United States	400	980	500	1,225

ND: no data; TWA: time-weighted average; STEL: short-term exposure limit.

For *n*-propanol and isopropanol, 15 min short-term exposure levels (STEL) of 250 ppm and 500 ppm have been added, respectively. In France, the same TWA limits for ethanol, *n*-propanol and isopropanol have been recommended, and a 15 min STEL of 5,000 ppm for ethanol has been proposed. Whereas acute and chronic health effects resulting from alcoholic beverage consumption are well known, there is a lack of knowledge regarding exposure via the inhalation and dermal routes. Despite intensive use of ABHRs in health-care, and peoples' growing interest in these products, only a few studies have addressed the issue of alcohol intake during hand rubbing procedures [15,66]. Kramer *et al.* [15] assessed the ethanol absorption level during hand hygiene and surgical disinfection procedures. They have tested three ABHRs containing 95 % and 85 % w/w ethanol, and 55% w/w ethanol with 10% w/w *n*-propanol. The authors reported that the total amount of alcohol absorbed ranged from 358 to 1,365 mg and from 477 to 1,542 mg, respectively, after 20 hygienic and 10 surgical hand disinfections. Miller *et al.* [66] have also investigated blood ethanol concentrations before and after 50 applications of 5 mL of 62 % ethanol products in five volunteers. They have observed a blood ethanol level lower than 50 mg/L in all five participants. Both studies have concluded that ethanol absorption is below the toxic levels for humans.

These studies on blood ethanol concentrations resulting from intensive hand rub applications over a limited period of time [15-66] have in common one major limitation, the use of only ethanol-based hand rubs, whereas, as described in Section 2, most sanitizers used nowadays are made up of at least two different alcohols, typically ethanol and isopropanol, the latter producing irritation of the respiratory system and damage to the central nervous system, and being classified in Group 3 by IARC [62-64].

Finally, a simple theoretical mass balance calculation of isopropanol during hand rubbing can be considered, as proposed by Kramer *et al.* [15] (this could be extended to other alcohols). If for example a health-care worker applies 90 mL (3 mL × 30 daily hand rubs) of a 70% w/w isopropanol hand rub per shift, a maximum of 67 g will evaporate into the air. If no air exchange takes place in a 12 m^3 room, a maximal isopropanol concentration of 5,500 mg/m^3 in air will result, which is approximately five times above the recommended occupational TWA (980 mg/m^3). This calculation is the worst case based on lack of air movement. Nowadays, hospital facilities have air movement from

heaters and air conditioners blowing air. However, this result shows that there is a need to characterize indoor air contamination close to users, assessing spatial and temporal variability of alcohols in air. Evaporation of alcohols during hand disinfection is a localized discontinuous source of pollution and may lead to a continuous and diffuse background contamination in intensive rubbing rooms, so ABHR users might be exposed during hand rubbing to passive alcoholization.

6. Conclusions

Ingestion of alcohol (ethanol) is well known to cause adverse health effects such as liver cirrhosis, fetal alcohol syndrome and cancer, but there is no evidence to suggest intoxication or dependence could occur with use of ABHRs. The only issue of passive alcoholization would relate to its biochemical effects. In addition, the use of ABHRs in healthcare settings as part of a hand hygiene program has a definable, clear-cut value, while the questions being raised in this article are preliminary and the answers are far from being settled.

In a context of an increased use of ABHRs, the issue of exposure to alcohols mainly via inhalation but also through dermal absorption should be considered to determine how safe air is. Despite the existence of a few studies, there is a general lack of knowledge about alcohol, especially *n*-propanol and isopropanol, contamination levels in the environment of ABHR users such as health care workers. Thus, more research is needed for contamination assessment, including spatial and temporal variability of alcohol emissions from ABHRs to indoor air (peak *vs* average concentrations) in real world situations. In addition, the sampling and analysis of alcohols and related metabolized by-products in exhaled air of non-drinkers might be used as an exposure biomarker, as a complement to serum alcohol levels. The next layer of studies could be performed on individuals with known liver disease to see if their ability to detoxify minute amounts of alcohol would put that at special risk. These data could improve our knowledge about exposure to alcohols through the inhalation route linked to the frequent use of ABHRs, in order to be able to propose recommendations such as increases in the air exchange rate within healthcare settings, if needed.

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Adapalene Submission

1. Adapalene Datasheet states that it is from a class of compounds known to cause photoallergic reactions and potentially increase the risk of skin cancers. We remind the MCC of their decision to classify ketoprofen gel as Prescription Medicine because of the risk of photoallergic reactions when other agents were already available without this potentially serious side effect.
2. Photoallergic reactions have been reported for adapalene and there is a multitude of acne preparation available at pharmacy level which lack this potentially serious side effect. Therefore adapalene should remain a Prescription Medicine.
3. Adapalene is a retinoid which are associated with teratogenic properties and stringent measures must be taken to ensure that teenagers at risk of pregnancy DO NOT use these products. It is therefore of paramount importance that these products are kept under the control of medical practitioners that know the medical history of the patient and have a confidential rapport with them.

Pediatric Focused Safety Review: Differin® (adapalene)

Pediatric Advisory Committee Meeting
May 7, 2012

Erica D. Radden, MD

Pediatric and Maternal Health Staff
Office of New Drugs

Center for Drug Evaluation and Research
Food and Drug Administration

Outline

- Background Information
- Pediatric Studies
- Pediatric Labeling Changes
- Additional Relevant Safety Labeling
- Drug Use Trends
- Adverse Events
- Summary

Background Drug Information
Differin® (adapalene)

- **Drug:** Differin® (adapalene)
- **Formulation:** lotion, 0.1%
- **Indication:** Topical treatment of acne vulgaris in patients 12 years and older.
- **Dosage and Administration:** Apply a thin film to the entire face and other affected areas of the skin once daily
- **Therapeutic Category:** Topical retinoid
- **Sponsor:** Galderma Research and Development, Inc.

Background Drug Information (continued)
Differin® (adapalene)

- **Original Market approval:** March 17, 2010
- **PREA labeling changes:** March 17, 2010
  - PREA studies waived in patients less than 12 years old
- Additional pediatric study requested for pharmacokinetic data under maximal use conditions in adolescents age 12-17 years (due Feb 2012).

Background Drug Information (continued) Differin® (adapalene)

- **Related product:** Epiduo® (adapalene/benzoyl peroxide) originally approved December 8, 2008

- **Other Approved Differin® formulations:**
  - Topical solution 0.1% (discontinued) (approved May 31, 1996)
  - Topical gel 0.1% (approved May 31, 1996)
  - Topical cream 0.1% (approved May 26, 2000)
  - Topical gel 0.3% (approved June 19, 2007)

Pediatric Studies: Safety and Efficacy Differin® (adapalene)

- Two 12-week multicenter, randomized, double-blind, vehicle-controlled, parallel group studies in patients 12 years of age and older with moderate to severe acne vulgaris.
- Patients randomized to Differin® lotion or vehicle
  - Study 1 (n=1075, age 12-50; n=670, age 12-18)
  - Study 2 (n=1066, age 12-64; n=674, age 12-18)
  - Median age (both studies): 16.7 years
- Differin® lotion demonstrated superiority over vehicle in decline of Investigator Global Assessment and lesion count from baseline.

Pediatric Labeling Changes Differin® (adapalene)

8.4 Use in Specific Populations, Pediatric Use

– Safety and effectiveness in pediatric patients less than 12 years have not been established.

Pediatric information included throughout labeling for patients 12 years and older.

Relevant Safety Labeling
Differin® (adapalene)

4 CONTRAINDICATIONS: none

5 WARNINGS AND PRECAUTIONS:

5.1 Ultraviolet Light and Environmental Exposure – Avoid exposure to sunlight, including sunlamps. Wear sunscreen and protective apparel when sun exposure cannot be avoided. Weather extremes, such as wind or cold may be irritating.

5.2 Local Cutaneous Reactions - erythema, scaling, dryness, and stinging/burning may occur.

Relevant Safety Labeling
Differin® (adapalene)

6 ADVERSE REACTIONS (AR):

System Organ Class/Preferred Term	Adapalene Lotion 0.1% N=1068	Vehicle Lotion N=1073
Subjects with Related AR(s)	10.2%	4.6%
Dry skin	7.7%	3.0%
Skin irritation	1.5%	0.7%
Skin burning/skin discomfort	0.9%	0.0%
Sunburn	0.6%	0.6%

*The majority of cases were transient, mild to moderate in severity and were managed with moisturizers.

Relevant Safety Labeling, Differin® (adapalene)

6 ADVERSE REACTIONS (continued):

Incidence of Local Cutaneous Irritation for Subjects Whose Irritation Score was Higher than at Baseline, in Controlled Clinical Studies (Differin® Lotion Group N=1057*)

Combined Study 1 and Study 2	Maximum Severity During Treatment (N=1057)			Week 12 Treatment Severity (N=950)		
Local Cutaneous Irritation (skin irritation)	Mild	Moderate	Severe	Mild	Moderate	Severe
Erythema	21.8%	8.0%	0.2%	7.9%	2.6%	0.2%
Scaling	25.3%	6.5%	0.1%	5.3%	1.1%	0
Dryness	36.1%	7.3%	0.3%	7.6%	2.0%	0
Stinging/burning	22.1%	7.0%	0.9%	4.6%	1.0%	0.4%

* Data from 11 subjects with missing data are not included

Local tolerability scores for the above symptoms rose during the first two weeks of treatment and generally decreased thereafter.

Adapalene-Containing Products* Drug Utilization[1]
Outpatient Retail Pharmacies
March 1, 2010 through December 31, 2011

	All Adapalene-Containing Products	
	Prescriptions (N)	Patients (N)
Total Population	3.4 million	1.9 million
Pediatric Population (0-16 years)	1.4 million	819,000

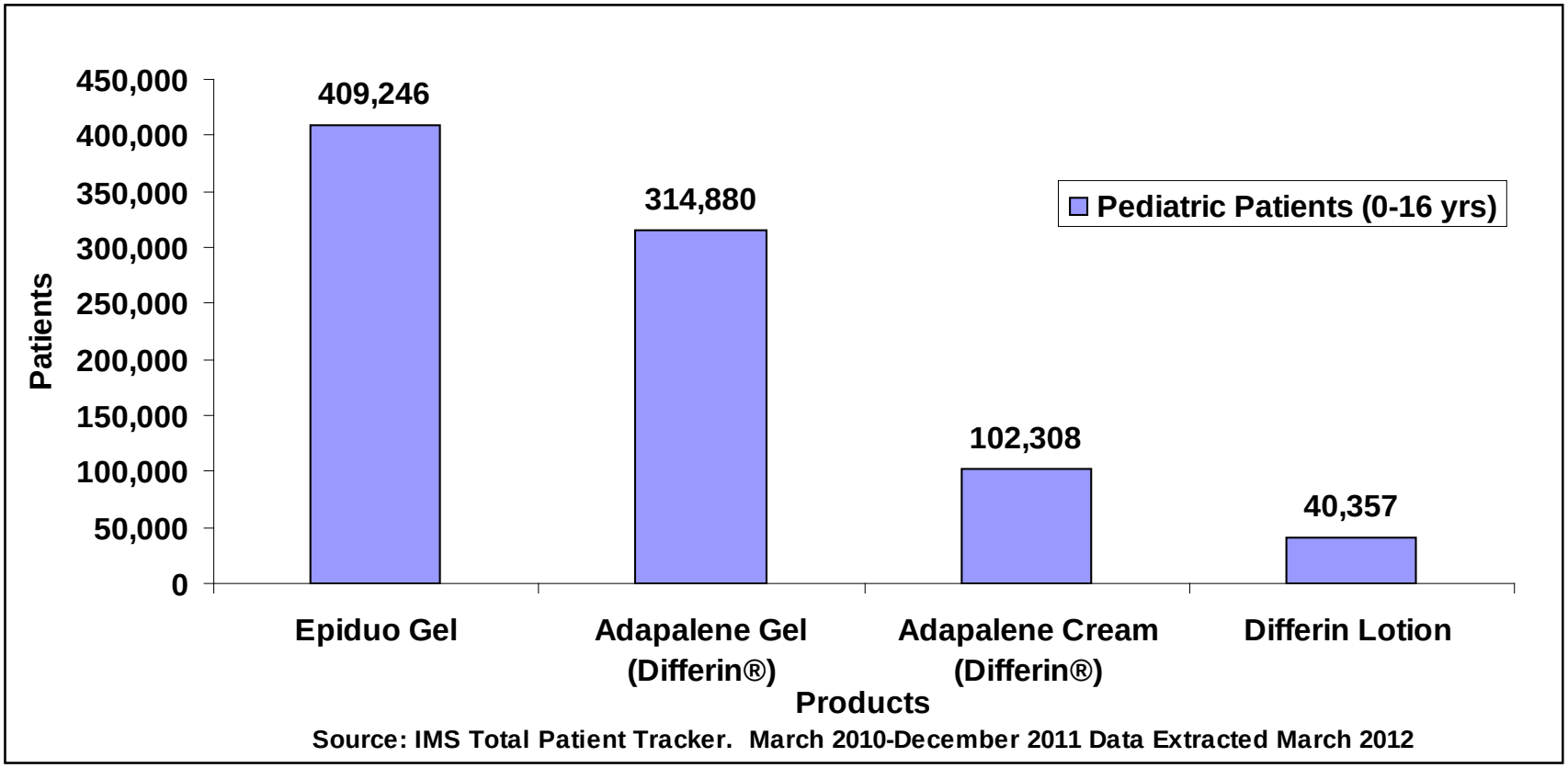
	Differin® Lotion	
	Prescriptions (N)	Patients (N)
Total Population	128,000	97,000
Pediatric Population (0-16 years)	53,000	40,000

*Adapalene-Containing Products include Epiduo Gel, Differin Gel, Adapalene Gel/Cream, Differin Cream, and Differin Lotion

[1]Source: IMS Vector One®: National and Total Patient Tracker, March 2010-December 2011 Data Extracted February 2012.

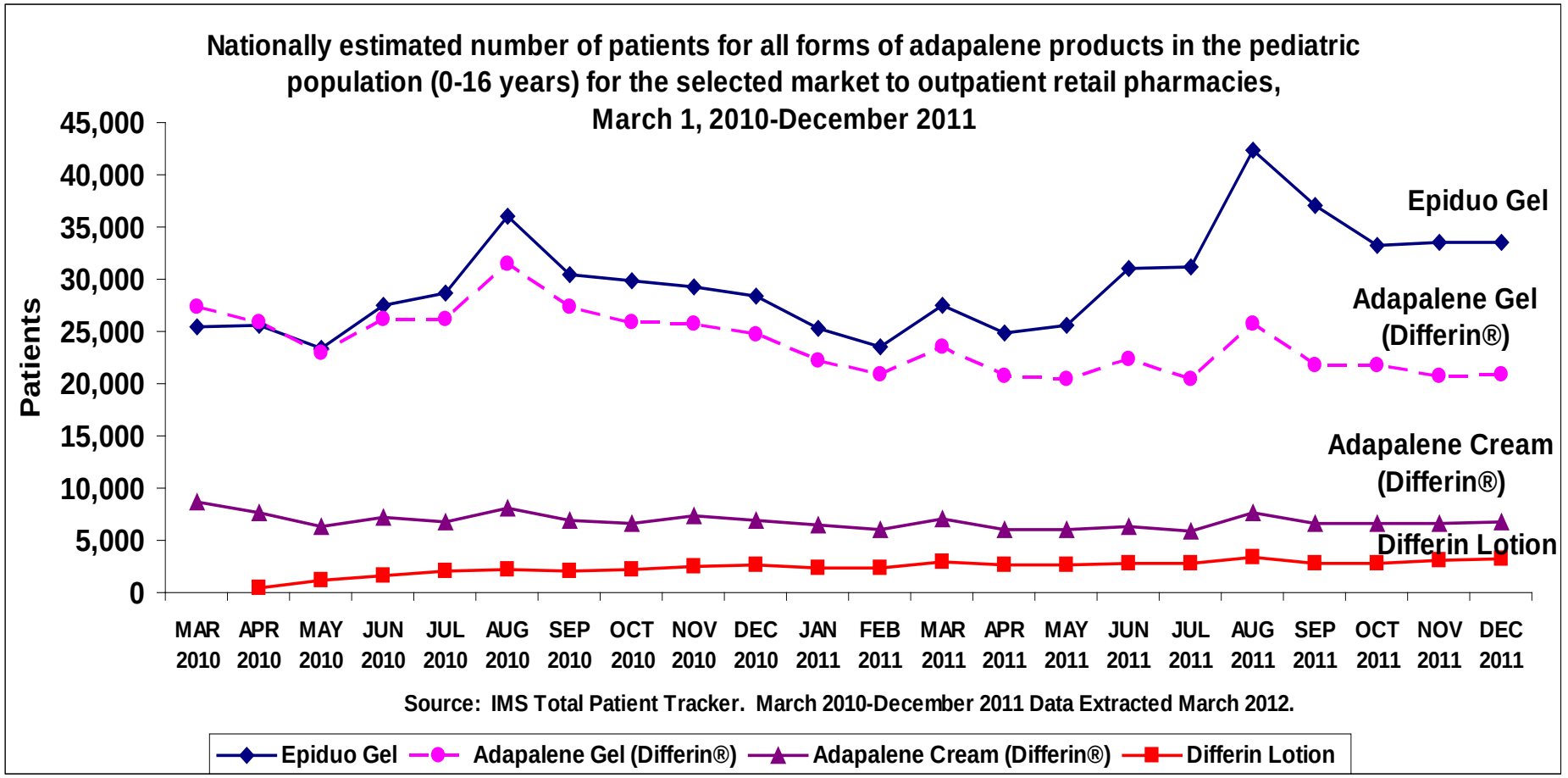
Adapalene-Containing Products Utilization by Product Formulation[1]

Nationally estimated number of pediatric patients (ages 0-16 years) who filled a prescription for Adapalene-containing products in U.S. outpatient retail pharmacies, March 1, 2010 - December 31, 2011



Source: IMS Total Patient Tracker. March 2010-December 2011 Data Extracted March 2012

Adapalene-Containing Products Drug Utilization Trends[1]



Differin® Lotion Drug Utilization Outpatient Retail Pharmacies March 1, 2010 through December 31, 2011

- Dermatology was the top prescribing specialty for Differin® Lotion (64% of prescriptions).[1]
  - Pediatricians accounted for 4% of prescriptions dispensed
- Top diagnosis code in pediatric patients aged 0-16 years was “Acne Not Elsewhere Classified” (ICD-9 706.1).[2]

[1]Source: IMS Vector One®: National, March 2010-December 2011 Data Extracted February 2012.

[2]Source: SDI Physician Drug and Diagnosis Audit, March 2010-December 2011 Data Extracted February 2012.

Previous Safety Reviews adapalene

- July 24, 2009. Phototoxicity with adapalene and tetracycline/doxycycline.
  - One report of phototoxicity in a 16 year old patient on multiple medications was identified, but timing of administration of tetracycline and adapalene could not be determined.
  - No action was recommended as a result of the review.

- August 30, 2010. Epiduo® post-marketing adverse event reports in patients 16 years of age and younger.
  - Labeling change recommended: add hypersensitivity-related adverse event information to the Contraindications and Postmarketing Experience sections of the Epiduo® label.

Epiduo® Pediatric Focused Safety Review

- Summary
  - The Epiduo safety review at the Pediatric Advisory Committee (PAC) on Dec. 7, 2010 identified the concern of an association of Epiduo® with hypersensitivity reactions
  - The PAC advised the FDA to revise labeling to include the potential for patient hypersensitivity to the product (PAC vote: 12 yes; 0 No; 0 Abstain; 1 committee member recused)
  - Labeling changes describing cutaneous reactions including irritant and allergic contact dermatitis added to:
    - 5.2 Local Cutaneous Reactions
    - 6.2 Postmarketing Experience

Epiduo® Labeling Changes*

- **5.2 Local Cutaneous Reactions:**
  Erythema, scaling, dryness, and stinging/burning may be experienced with use of EPIDUO gel. These are most likely to occur during the first four weeks of treatment, are mostly mild to moderate in intensity, and usually lessen with continued use of the medication. Irritant and allergic contact dermatitis may occur. Depending upon the severity of these adverse reactions, patients should be instructed to use a moisturizer, reduce the frequency of the application of EPIDUO gel, or discontinue use. The product should not be applied to cuts, abrasions, eczematous or sunburned skin. As with other retinoids, use of "waxing" as a depilatory method should be avoided on skin treated with EPIDUO gel. Avoid concomitant use of other potentially irritating topical products (medicated or abrasive soaps and cleansers, soaps and cosmetics that have strong skin-drying effect and products with high concentrations of alcohol, astringents, spices, or limes).

- **6.2 Postmarketing Experience:**
  The following adverse reactions have been identified during postapproval use of EPIDUO Gel: eyelid edema, sunburn, blister, pain of skin, pruritus, swelling face, conjunctivitis, skin discoloration, rash, eczema, throat tightness and allergic contact dermatitis**.**

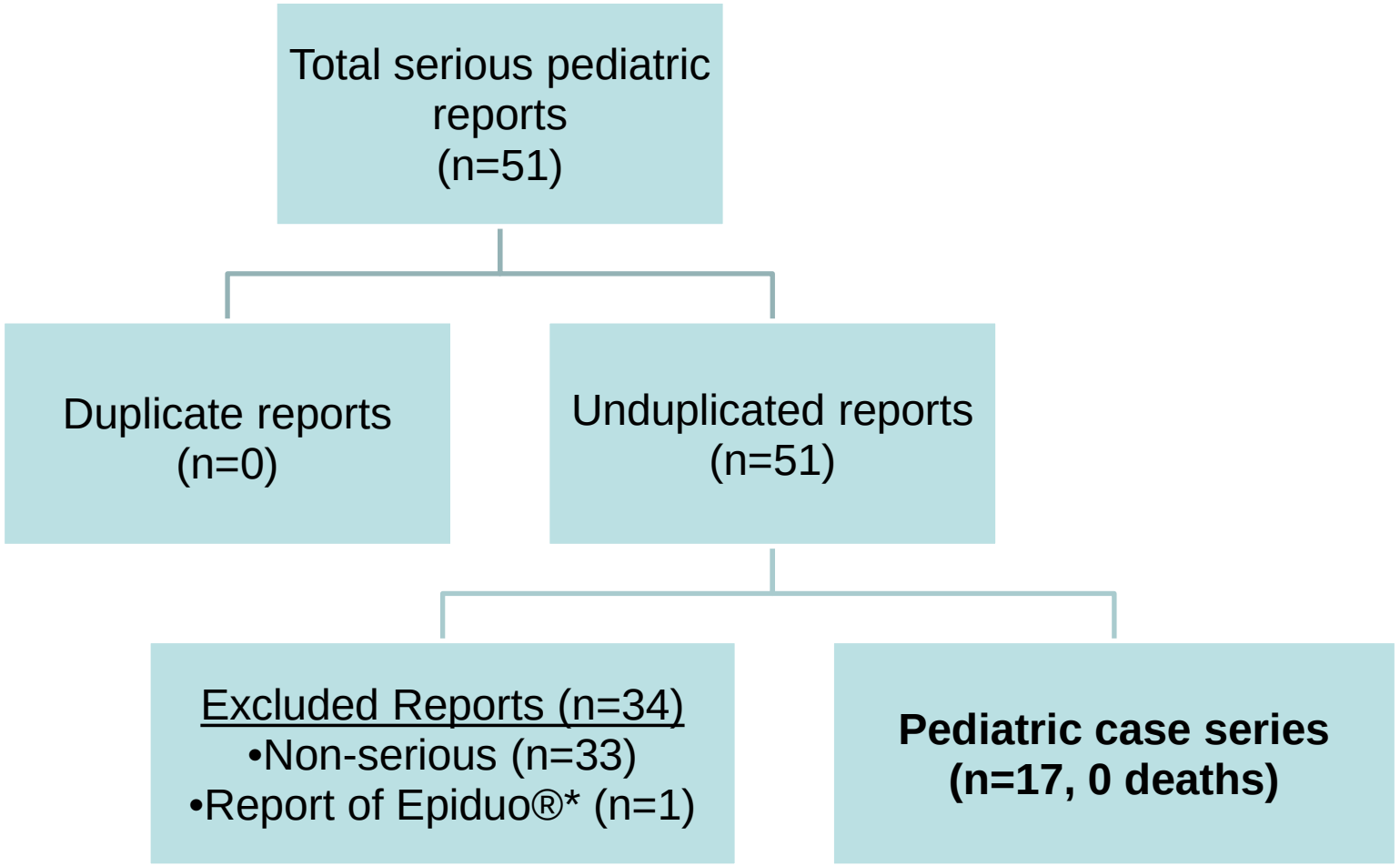
*Labeling changes are underlined.

Total Number[1] of Differin® Adverse Event Reports Since Pediatric Approval[2] (May 31,1996 to January 3, 2012)

	All reports (US)[3]	Serious[4](US)	Death (US)
Adults (≥ 17 yrs.)	107 (83)	95 (71)	0 (0)
Pediatrics (0-16 yrs.)	54 (41)	**51 (39)**	0 (0)
Unknown Age (Null values)	55 (42)	50 (39)	0 (0)
All Ages	216 (166)	196 (149)	0 (0)

[1]May include duplicates and have not been assessed for causality
[2]Search included Differin, adapalene, and all associated verbatim names from date of first Differin® formulation approval, May 31, 1996.
[3]US counts in parentheses
[4]Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening events, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.

Case Selection- Serious Adverse Events



* Report captured in previous Epiduo® PREA review.

Characteristics of Serious Pediatric Cases Differin® (adapalene) (n=17)

- Gender
  - Male (n=8)
  - Female (n=9)
- Age
  - Birth - 1 month (n=2)
  - 2 months - 1 year (n=0)
  - 2 - 5 years (n=1)
  - 6 - 11 years (n=1)
  - 12 - 16 years (n=13)

Serious Non-Fatal Adverse Events Differin® (adapalene) (n=17)

- Dermatologic (n=6)
  - 3 labeled, 3 unlabeled
- Central Nervous System (n=5)
  - All unlabeled
- Hepatobiliary (n=3)
  - All unlabeled
- Congenital Anomalies (n=3)
  - Pregnancy Category C

Serious Non-Fatal Labeled Adverse Events Differin® (adapalene)

Dermatologic - labeled (n=3)

- 16 year old female experienced a photoallergic reaction 6 days after re-initiating topical clindamycin and adapalene (formulation not specified), which improved following treatment with steroids. She had used both medications previously for one year.
- 15 year old male using adapalene gel 0.3%, clindamycin/benzoyl peroxide combination and an unspecified facial cleanser reported application of adapalene “felt funny” resulting in occasional non-compliance.
- 13 year old female with a history of atopy experienced acute contact eczema after her second application of adapalene cream 0.1%. Skin biopsy was performed in the emergency room, but results were not reported.

Labeling - WARNINGS AND PRECAUTIONS: avoid sun exposure; ADVERSE REACTIONS: dermatitis, contact dermatitis, eczema

Serious Non-Fatal Unlabeled Adverse Events Differin® (adapalene)

Dermatologic (n=3)

- 10 year old female developed ecchymotic spots on her face 2 months after initiation of adapalene cream 0.1%, that were believed to be erythema multiforme. She was instructed to discontinue the adapalene, but did not return for follow-up.
- 16 year old male using adapalene (formulation not specified) for approximately 1 year experienced thinning of the hair and receding of the hairline. Concomitant medications: fexofenadine and esomeprazole for an unknown period of time.

Esomeprazole (Nexium®) labeling - ADVERSE REACTIONS: alopecia

*Unlabeled events are underlined

Serious Non-Fatal Unlabeled Adverse Events Differin® (adapalene)

Dermatologic (n=3) (continued)

- 16 year old female experienced angioedema 13 days after the initiation of minocycline and adapalene gel 0.1%. Laboratory studies revealed a WBC of 13,800 cells/microliter and a positive Mycoplasma titer. She was hospitalized and improved with discontinuation of the minocycline and adapalene and treatment with prednisolone and furosemide.

Minocycline (Minocin) labeling - ADVERSE REACTIONS: Hypersensitivity reactions: angioneurotic edema.

Mycoplasma is associated with urticaria and angioedema.[1,2]

*Unlabeled events are underlined.

[1]Shah KN, Honig PJ, and Yan AC. "Urticaria Multiforme": A Case Series and Review of Acute Annular Urticarial Hypersensitivity Syndromes in Children. *Pediatrics*. May 2007;119(5):e1177-83.
[2]Stockner I, Thaler J, Fichtel F, Egarter-Vifl E, Wallnofer W, Wiedermann CJ. Non-episodic angioedema associated with eosinophilia following Mycoplasma pneumoniae infection. *Clin Rheumatol*. Dec 2008;27(12):1573-6.

Serious Non-Fatal Unlabeled Adverse Events Differin® (adapalene)

Central Nervous System (n=5)
Neuropsychiatric Events (n=1)

- 16 year old male developed "lack of concentration, trouble focusing, trouble sleeping, anxiety and was dispirited and depressed" 7 months after initiation of adapalene gel 0.3% and an unknown time after initiation of a clindamycin/benzoyl peroxide topical combination product. He recovered 1 month after discontinuation of adapalene. Clindamycin/benzoyl peroxide was continued.

*Unlabeled events are underlined.

Serious Non-Fatal Unlabeled Adverse Events Differin® (adapalene)

Central Nervous System (n=5) (continued)

Neuromuscular Events (n=1)

- 16 year old female developed ptosis, muscular weakness, and difficulty swallowing 3 months after initiating treatment with oral lymecycline, and topical erythromycin and adapalene gel (unspecified strength).

  While being evaluated, topical tretinoin was substituted for adapalene secondary to lack of efficacy, and 2 months later all acne medications were discontinued and replaced with an erythromycin/benzoyl peroxide combination.

  She was diagnosed with myasthenia gravis, and responded to treatment with thymectomy and pyridostigmine.

*Unlabeled events are underlined.

Serious Non-Fatal Unlabeled Adverse Events Differin® (adapalene)

Central Nervous System (n=5) (continued)

General CNS Events (n=3)

- 14 year old female (60 kg) hospitalized with intracranial hypertension after using adapalene gel 0.1% (unspecified duration). Lumbar puncture detected no infection. Resolution without sequelae; it is unclear if adapalene was discontinued.

- 13 year old female (weight not specified) developed blurred vision and headaches approximately 1-2 months after starting adapalene gel (unspecified strength). Increased pressure on the optic nerve was noted by Ophthalmology and her lumbar puncture revealed elevated intracranial pressure. Adapalene was discontinued and her headaches improved.

*Unlabeled events are underlined.

Serious Non-Fatal Unlabeled Adverse Events Differin® (adapalene)

Central Nervous System (n=5)

General CNS Events (n=3) (continued)

- 14 year old female (48 kg) developed headache, nausea, vomiting, blurred vision, numbness and tingling in extremities and CN VI palsy 5 days after starting minocycline and adapalene gel (unspecified strength). Papilledema was noted and she was diagnosed with drug-induced pseudotumor cerebri. After initial improvement on acetazolamide, symptoms worsened, and she was hospitalized. Lumbar puncture revealed an elevated opening pressure with normal CSF cell count and culture. MRI was normal. Furosemide was added to acetazolamide with improvement following discontinuation of minocycline and adapalene.

Minocycline (Minocin) labeling - PRECAUTIONS: pseudotumor cerebri (benign intracranial hypertension).

Idiopathic Intracranial Hypertension is associated with hypervitaminosis A and is labeled for the systemic, but not the topical retinoids.

* Unlabeled events are underlined.

Serious Non-Fatal Unlabeled Adverse Events Differin® (adapalene)

Hepatobiliary (n=3)

- A 16 year old male taking adapalene (formulation not specified) for an unknown duration and isotretinoin for 1 day was noted to have elevated transaminase levels on screening labs for initiation of isotretinoin. Liver biopsy showed globular hepatic lesions. Adapalene was discontinued. Follow-up information was not provided.

Isotretinoin labeling - ADVERSE REACTIONS: mild/moderate elevations of liver enzymes

*Unlabeled events are underlined.

Serious Non-Fatal Unlabeled Adverse Events Differin® (adapalene)

Hepatobiliary (n=3)

- 15 year old male with prior history of unspecified drug allergy and Haemophilus meningitis was hospitalized with cholestatic jaundice and hepatitis 2 months after the initiation of topical adapalene gel 0.1% and oral minocycline. Anti-HCV antibodies were positive. Biopsy indicated cholestasis with cytolysis. Treatment status for the HCV was not reported. Improvement was noted 5 months following discontinuation of both drugs.

Minocycline labeling - WARNINGS AND PRECAUTIONS: hepatotoxicity; ADVERSE REACTIONS: hepatic cholestasis, hepatitis

*Unlabeled events are underlined.

Serious Non-Fatal Unlabeled Adverse Events Differin® (adapalene)

Hepatobiliary (n=3) (continued)

- 15 year old male with history of pneumonia and no significant family medical history developed acute liver failure while using adapalene gel 0.1% for 6 months and taking erythromycin 250 mg daily for an unknown period of time. Abdominal ultrasound, renal function, and viral hepatic serologies were normal. Wilson's disease, autoimmune disease, metabolic disease and alpha-1-antitrypsin deficiency were ruled out. Symptoms persisted despite discontinuation of adapalene and liver transplantation was considered.

Erythromycin labeling - WARNINGS and ADVERSE REACTIONS: hepatic dysfunction

*Unlabeled events are underlined.

Serious Non-Fatal Unlabeled Adverse Events Differin® (adapalene)

Congenital Anomalies (n=3)

- A male neonate whose mother had applied adapalene gel 0.1% twice during her pregnancy was born with one kidney.
- 4 year old male, whose mother used adapalene throughout pregnancy, was diagnosed with neurofibromatosis type 1 (NF1).
- A male neonate whose mother used adapalene gel (unspecified strength), clindamycin, and a topical antifungal liquid for the first 2-4 weeks of pregnancy was born with multiple birth deformities, including Scimitar syndrome, Dandy-Walker malformation, atrial septal defect and merged kidneys. No chromosomal abnormalities were detected.

These 3 reports were analyzed in previous adapalene safety reviews.

Relevant labeling: Adapalene is pregnancy class C

* Unlabeled events are underlined.

Pediatric Focused Safety Review Summary Differin® (adapalene)

- This concludes the pediatric focused safety review
- As a result of PREA studies, adapalene lotion is approved in patients 12 years and older.
- The safety review identified 3 cases of Idiopathic Intracranial Hypertension (IIH); all involved the gel form.
- FDA is conducting a review of IIH and topical retinoids in all ages. No modification of the adapalene labeling is recommended at this time.
- Does the Committee concur?

ACKNOWLEDGEMENTS

Division of Dermatology and Dental Products
Amy Woitach, MD
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J. Paul Phillips, MS

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Jessica Weintraub, PharmD
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Ethan D. Hausman, MD
Linda Scarazzini, MD, RPh

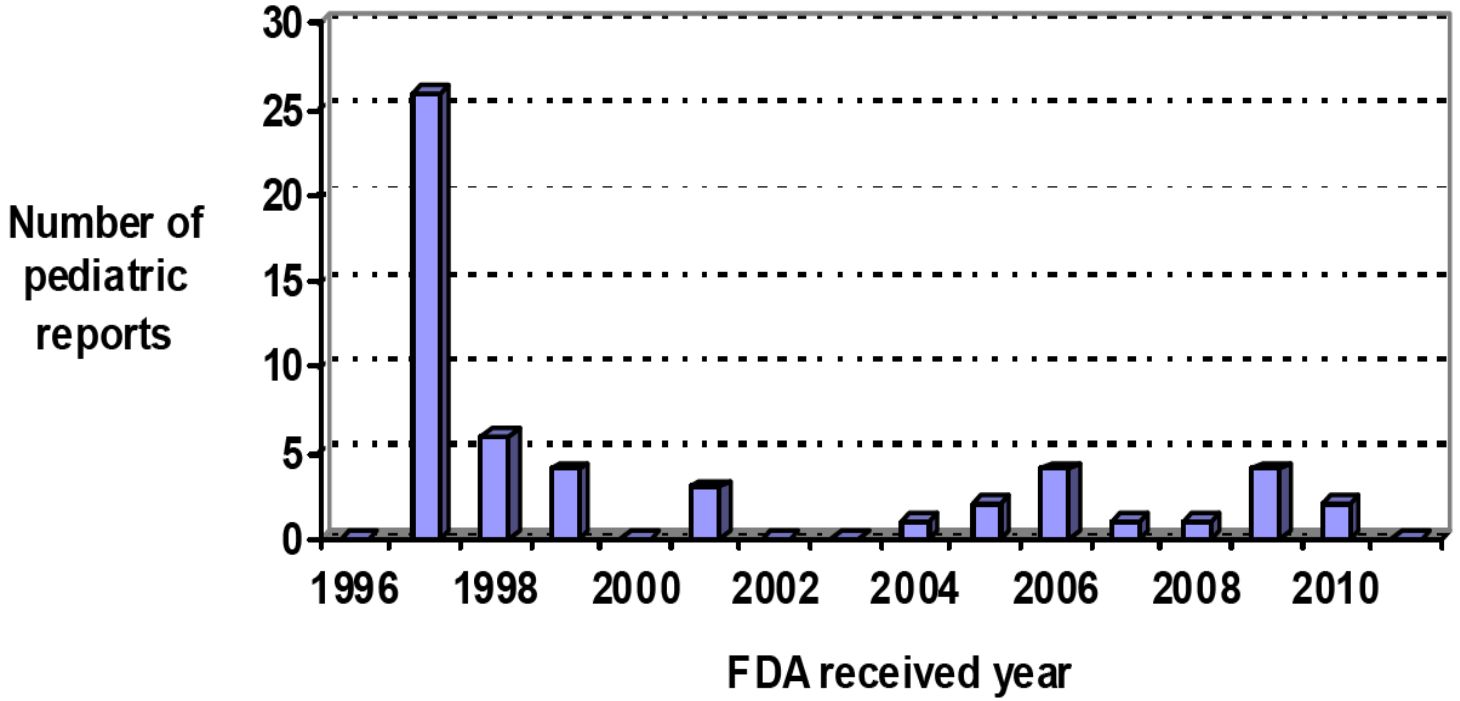
Previous Safety Reviews: Pregnancy Exposure adapalene

- May 18, 2004 (AERS and the literature)
  - Five cases of congenital anomalies.
  - Three considered potential cases of retinoid-specific birth defects.
  - No labeling changes were recommended.

- September 8, 2006 (Sponsor's information)
  - One additional case not included in the 2004 review was identified with multiple organ system anomalies that were not consistent with the usual picture of retinoid embryopathy.
  - Labeling change recommended: Add pregnancy outcome information to the label, consistent with other Pregnancy Category C topical retinoids.

Differin® Pediatric Adverse Event Reports (May 31,1996 to January 3, 2012)

Total number of Pediatric Reports (including serious and non-serious) for adapalene by year of FDA receipt (May 31, 1996 to January 3, 2012) (n=54)



* These numbers include data where age (0-16 years) is known and may contain duplicate reports.

16 March 2016

Albendazole – proposed reclassification from prescription to pharmacy-only medicine (Te Arai BioFarma Ltd)

I am writing to make comment on the proposal to reclassify albendazole from prescription medicine to pharmacy-only medicine.

Albendazole has a number of usages to an infectious diseases clinician. These indications include ascaris, hydatid disease, and strongyloidiasis. It therefore has a considerably wider indications than mebendazole considered due to systemic bioavailability. I believe that mebendazole is more appropriate to be maintained as the first line therapy for the common worm indications in NZ when we are mainly deal with pinworm. Having a second agent on pharmacy only is likely to lead to albendazole usage occurring over mebendazole (particularly if actively marketed by the supplier).

I have asked a colleague of mine with considerable experience in parasitology to comment. Dr Mark Thomas (ID physician, Auckland City Hospital) has stated:

"I cannot see a reason why albendazole should be available to purchase without a prescription. I find it hard to imagine that there is a demand from the public for such access and in general think that availability to purchase without a prescription has been an unfortunate decision with regard to a number of antimicrobials in NZ, Bactroban being a prime example."

As Chair of the anti-infective subcommittee pf PTAC, we had discussions on albendazole at a previous meeting on 22 February 2012. Our comments were:

"9.1 With respect to albendazole the Subcommittee considered this should be restricted to Infectious Disease physicians and Clinical Microbiologists. The Subcommittee noted that albendazole should be available on discharge for short term treatment of strongloidiasis, toxocariasis, ancylostomiasis, neurocysticerosis and schistosomiasis.

9.2 With respect to albendazole the Subcommittee considered this should be listed in the Community Pharmaceutical Schedule for the treatment of hydatids with a six month Special Authority with renewal."

I trust that this is helpful as you consider this submission.

Regards

Dr Graham Mills, Infectious Diseases Physician, Waikato Hospital and Chair of Anti-infective subcommittee of PTAC.

New Zealand Hospital Pharmacists' Association (Inc)
Te Kāhui Whakarite Rongoā Hōhipera O Aotearoa

05 April 2016

Medicines Classification Committee (MCC)
Medsafe
Ministry of Health
e: committees@moh.govt.nz

Re: Proposed classification of albendazole as a pharmacy-only medicine

Dear Committee,

On behalf of the NZ Hospital Pharmacists' Association, the Antimicrobial Stewardship Pharmacists are writing to state that we do not support the proposal to reclassify albendazole as a pharmacy-only medicine.

Availability of albendazole over-the-counter is not in keeping with antimicrobial stewardship as it encourages the unnecessary and inappropriate use of this agent, which potentially compromises its role in the treatment of refractory giardiasis, and hydatid disease. The company state that over-the-counter availability 'offers an alternative anthelmintic particularly when resistance is a concern'. Surely, individuals with suspected resistance (perhaps those who have failed treatment with an alternative over the counter anthelmintic) should undergo appropriate medical review to ensure accuracy of diagnosis e.g. with stool samples? Related to this, please note that there are actually two anthelmintic agents already available over-the-counter in New Zealand i.e. mebendazole and pyrantel pamoate, not one as stated in the application.

The application also seems to carry a mix of information relevant to single doses and longer courses. The company states that the 'albendazole has been in use worldwide for more than 30 years with no signals of unexpected or serious adverse events'. This is somewhat misleading as longer courses are linked with hepatic and myelotoxicity, which means that liver function and blood counts are monitored regularly during longer courses. We are unclear whether these toxicities are a significant risk if consumers elect to dose repeatedly e.g. if symptoms do not resolve after a single dose or they 'diagnose' symptoms incorrectly.

Unfortunately, there are also significant issues with the overall quality of this application with many inaccuracies and errors. Some of these are highlighted below:

- There are numerous inaccuracies and misleading statements within the application pertaining to the pharmacokinetics, adverse effects, interactions and

New Zealand Hospital Pharmacists' Association (Inc), Level 10, Grand Arcade Tower, 16-20 Willis Street, Wellington 6011
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contraindications/precautions of albendazole that indicates a lack of understanding of the pharmacology of this agent.

- The proposed packaging has spelling and grammatical errors, and implies pinworms and threadworms are different parasites.
- The application and the consumer information leaflet are unnecessarily frightening with respect to the risks of using albendazole in pregnancy, and do not match the published literature. Additionally, if the company believes women should have a negative pregnancy test prior to taking this drug, who do they propose will ensure this happens if it is available for self-selection?

In summary, we have substantial concerns about the proposed classification of albendazole as a pharmacy only medicine. However, we would support the move to have a registered albendazole product classified as a prescription medicine and to have community subsidy extended beyond treatment of hydatid disease, e.g. to refractory giardia with appropriate specialist endorsement. If the company propose attempting to register their product in New Zealand for this purpose we recommend that they involve an appropriate expert (clinical/pharmacological) in the development of their application.

Finally, if you have a mechanism for bringing potential changes to antimicrobial classifications to the attention of relevant parties, we would be grateful if our group could be included in the consultation process. Correspondence can be sent directly to the NZ Hospital Pharmacists' Association who will then forward the request onto the appropriate group.

Yours sincerely

NZ Hospital Antimicrobial Stewardship Pharmacists

Eamon Duffy, Auckland DHB
Jessica Rickard, Bay of Plenty DHB
Sharon Gardiner, Canterbury DHB
Brijul Morar, Capital and Coast DHB
Tanya DuPlessis, Counties Manukau DHB
Ben Robertson, Hawke's Bay DHB
Chris Little, Hutt Valley DHB
Nicola Williams, Waitemata DHB

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Australasian Society for Infectious Diseases (ASID) Inc
ABN: 20 108 151 093/ARBN: 155 632 698

The Medicines Classification Committee (MCC)
Medsafe
Ministry of Health

Via email: committees@moh.govt.nz
CC: Harriet.Wild@racp.org.nz

24 March 2016

Dear Committee

We are writing to express our concerns regarding the proposal to list Albendazole as a Pharmacy-only medication. The rationale behind this, as I understand, is to improve the coverage of resistant parasitic infections over what are currently treatable by Mebendazole.

Whilst this may be true, we have a number of concerns regarding the listing.

1. As a pharmacy-only medication, this would allow purchase 'off-the-shelf' by consumers with no requirement for medical or pharmacist input. Consumers targeted by the proposed changes would largely be immigrants and refugees (i.e. those at risk of resistant parasitic infections such as hookworm), who are less likely to have English as a first language and in whom it would be more important to have guidance in appropriate treatment.

2. It is recommended that "Albendazole should not be given to pregnant women or women thought to be pregnant and that effective contraception should be taken during and within one-month after treatment. Prior to starting treatment women of childbearing age should take a pregnancy test". Whilst these recommendations may be overly cautious, they currently stand. If Albendazole is available as a pharmacy-only' medication, who is going to ensure these recommendations are followed?

3. Albendazole remains an important component of treatment of hydatid disease, refractory giardiasis and other challenging parasitic infections and allowing more empiric usage has the potential for worsening resistance problems in general. Ideally patients should have a stool test to identify the presence of a parasitic infection prior to treatment.

4. We would recommend Albendazole be available as a prescription-only medication, restricted to Infectious Disease Physicians and Clinical Microbiologists who have expertise in treating such infections.

5. Finally, it would be very helpful in the future if there are any proposed changes in classification of antimicrobials, that notification and feedback to be actively sought from the relevant specialists. The proposal for Albendazole came to our attention via the College of General Practitioners. An appropriate forum for feedback from Infectious Disease Specialists and Clinical Microbiologists is via the New Zealand Branch of the Australasian Society of Infectious Diseases (ASID).

Yours sincerely,

Dr Kerry Read
Chair, New Zealand Branch
Australasian Society of Infectious Diseases (ASID) Inc.

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The Medicines Classification Committee (MCC)
Medsafe
New Zealand Ministry of Health

Via email: committees@moh.govt.nz

4 April 2016

Dear Committee

Re. Proposal to list Albendazole as a Pharmacy-only medication.

In addition to supporting all issues outlined in the letter dated 24 March 2016 from the Chair of the New Zealand Branch of ASID, Dr Kerry Read, we would like to raise an additional concern relevant to children.

Mebendazole and pyrantel are both currently available over the counter (and mebendazole is funded on prescription) for pinworm also known as threadworm. This is likely the most common intestinal parasite in NZ children. There are not resistance issues identified in pinworm. The efficacy of mebendazole and albendazole for pinworm appears equivalent.

Pinworm typically affects the toddler age group and no dosing for albendazole is given for those aged <6 years. Additional marketing for parasitic drugs to be available in pharmacy for "resistant" parasites (hookworm, ascaris) not seen in New Zealand has the potential to confuse and target consumers such as parents.

As indicated by Dr Read in her letter, it would be very helpful in the future if notification and feedback on any proposed changes in classification of antimicrobials were actively sought from the relevant specialists. An appropriate forum for feedback from Infectious Disease Specialists and Clinical Microbiologists is via the New Zealand Branch of the Australasian Society of Infectious Diseases (ASID) at admin@asid.net.au.

Yours sincerely

Dr Emma Best
Paediatric Infectious Diseases Specialist
Committee Member, ASID NZ Branch and ANZ Paediatric ID Group (ANZPID)
Chair, Infection and Immunisation Special Interest Group of the Paediatric Society of NZ

Professor Cheryl Jones
President, Australasian Society for Infectious Diseases (ASID) Inc.

Professor David Burgner
Chair, ASID's Australia and New Zealand Paediatric Infectious Diseases Group (ANZPID)

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Canterbury
District Health Board
Te Poari Hauora o Waitaha

Sharon Gardiner (Secretary)
Antimicrobial Stewardship Committee
C/- Infectious Diseases Department
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CDHB Antimicrobial Stewardship Committee

04 April 2016

Medicines Classification Committee
Medsafe
E: committees@moh.govt.nz

RE: APPLICATION FOR CLASSIFICATION OF ALBENDAZOLE 200 MG TABLETS AS PHARMACY ONLY MEDICINE IN DOSES NOT EXCEEDING 400 MG

Dear Committee,

Canterbury DHB's Antimicrobial Stewardship committee have discussed the above application and are writing to state that we do not support the availability of this albendazole over the counter. Our comments are below.

1. **Overall position on the application:**
   We do not support the availability of albendazole as a pharmacy only medicine for self-selection by consumers. Increased availability of antiparasitic agents with potential for inappropriate use is counter to the global mission for antimicrobial stewardship. It will potentially promote resistance and compromise its effect in conditions such as refractory giardia. Additionally, we believe that consumers with worms other than threadworms (pinworms) should undergo appropriate medical investigation rather than be encouraged to self-treat, perhaps repeatedly if the treatment is perceived as having failed. Inappropriate repeated administration exposes the patient to hepatic injury and myelotoxicity, which is seen rarely during longer courses.

   While we do not support the availability of albendazole over the counter, we do support the availability of a registered formulation of albendazole that is subsidised and able to be prescribed for appropriate indications by authorised prescribers. We agree with the requirement to have Infectious Diseases/Clinical Microbiology recommendation for the use in Section H of the Pharmaceutical Schedule, and support its availability by Specialist Authority for hydatid disease in the community. It would also be helpful if it was subsidised for refractory giardia, with appropriate medical specialist endorsement.

2. **Quality of the application:**
   There were multiple errors within the application that imply a fundamental lack of understanding about the pharmacology of this agent. This application would have benefitted from review by an appropriately qualified person skilled in pharmacology. Some of the errors/issues are outlined below:
   - Introduction, page 2, para 2. Both albendazole (gut) and albendazole sulfoxide (tissue) are pharmacologically active (text implies only the metabolite is active). The statements that albendazole is 'poorly absorbed (< 5%)' and 'almost exclusively eliminated by the liver' do not align.
   - Introduction, page 2, para 3. The statements '~20% systemic absorption and rapid first-pass liver metabolism' appear not to match up with 'approximately 95% is excreted unchanged in the faeces' (mebendazole) and requires clarification.
   - Overview, page 2, para 1. It is 'reimbursed under s29 of the Medicine Act' (underlined text = incongruent).
   - Conclusion, page 4, para 1. 'Albendazole has been in use worldwide for more than 30 years with no signals of unexpected or serious adverse events, and offers an alternative anthelmintic particularly when

resistance is a concern'. How do reports of liver and bone marrow toxicity fit in with this statement? The second part of the statement (re: resistance) argues against widening the access to enable self-selection.

- PART A, page 6, Indications for which change is sought. Pinworms = threadworms (different lay name for the same worm).
- PART A, page 7, Proposed warning statements if applicable:
  a. Pregnancy. Statements like 'should not be given to pregnant women...' and 'women of childbearing age should take a pregnancy test' before starting treatment throughout the application and consumer information are not consistent with published data (which extends beyond the 17 women described).
  b. Breastfeeding. 'Albendazole should not be used while breastfeeding' does not reflect the low infant dose in milk (< 2% of the maternal dose, corrected for weight) nor the belief that organisations such as WHO consider a single dose compatible with breastfeeding.
  c. 'Caution should be exercised in treating people with liver disease'...why?
  d. 'Care should be taken in patients taking oral contraceptives, anticoagulants, oral diabetes medications or theophylline'. Why?
- PART B, page 7, Benefit to consumer/public. There are two anthelmintics already available OTC in NZ i.e. pyrantel pamoate (Combatrin) and mebendazole. Availability of a third agent for over the counter self-selection that may have value in refractory or resistant parasitic infections is not appropriate. Failure to respond to a first line agent requires further investigation.
- PART B, page 11, Interactions with other medicines. The text implies a misunderstanding about whether albendazole is a substrate or inducer of P450 enzymes (note that these are not all in the liver). It is not adequate to refer to 'anticonvulsants' in this respect since agents within this class vary in their effects on this enzyme system.

Appendix 1: Proposed labelling. This requires work – there are multiple spelling/grammatical errors; Threadworms and pinworms are two lay names for the same parasites (not two distinct types of worms).

NZ Consumer Medicine Information leaflet. Some of the text inappropriately implies that the product has been prescribed by a doctor or pharmacist, whereas the 'pitch' here is for self-selection over the counter, albeit in a pharmacy where advice can be sought. Pregnancy and breastfeeding cautions are inconsistent with the evidence. Adverse effects – what about including a statement to put perspective on the adverse effects such as 'A single dose of albendazole is usually well tolerated with no difference in adverse effects compared with placebo (dummy) tablets'.

To summarise, we do not support this application to have albendazole available over the counter due to consumer risks and the potential to compromise its use for other indications. The pharmacological aspects of the application contain many errors as well as misleading statements.

Yours sincerely,

Professor Steve Chambers
Infectious Disease Physician

Dr Sarah Metcalf
Infectious Diseases Physician

Dr Sharon Gardiner
Antimicrobial Pharmacist

4 April 2016

MCC Secretary
Medsafe
PO Box 5013
WELLINGTON 6145

Email: committees@moh.govt.nz

Dear Sir/Madam

PROPOSAL TO CHANGE THE CLASSIFICATION WORDING FOR VARIOUS RESTRICTED AND PHARMACY ONLY MEDICINES
MEDICINES CLASSIFICATION COMMITTEE (MCC) 55TH MEETING AGENDA: ITEM 6.5

The New Zealand Food & Grocery Council (the "NZFGC") welcomes the opportunity to comment on the proposal contained in Item 6.5 of the MCC55 Agenda: ***Change in classification wording of lansoprazole, promethazine, sumatriptan, ibuprofen, omeprazole, pantoprazole, opium, pholcodine and ranitidine – proposed change in classification wording (Pharmaceutical Society of New Zealand)***.

NZFGC represents the major manufacturers and suppliers of food, beverage and grocery products in New Zealand. This sector generates over $34 billion in the New Zealand domestic retail food, beverage and grocery products market, and over $31 billion in export revenue from exports to 195 countries – some 72% of total merchandise exports.

Comments

NZFGC is strongly opposes the proposal advocated by the Pharmaceutical Society of New Zealand Inc (PSNZ). We support the submission made by the New Zealand Self-Medication Industry and concur with the following concerns:

- Safety – This is the highest priority for medicines, regulated through stringent approval processes, mandatory labelling and additional pack inserts and consumer information leaflets that protect and provide necessary information to consumers about a product.

  The PSNZ proposal would result in pharmacies in New Zealand bypassing the detailed mandated product labelling required of product sponsors. The proposal would jeopardise post market surveillance since this would not be a sponsor led activity.

- Standardisation and uniformity – with over 900 pharmacies in New Zealand, presentation, uniformity and product information would be severely compromised under

the PSNZ proposal. Inevitably, a variety of different practices would emerge with limited opportunity for audit and calibration to be undertaken by any external agency.

- Traceability – In approving a pack for over the counter supply, Medsafe is able to ensure the necessary and mandated batch labelling requirements are met. These are critical for accurate traceability in the event of a recall of a particular product. If the supply of a product is permitted along the lines proposed by the PSNZ, recall of particular packs through batch number identification from the supplier would not be possible.

- Advertising products – there are significant benefits for consumers from the product advertising undertaken by product sponsors. Advertising and the associated education of consumers on products, would likely decrease over time, disadvantaging New Zealand consumers.

NZFGC is concerned that the PSNZ proposal would jeopardise consumer safety, compromise standardisation and uniformity, threaten traceability and undermine the high standard of presentation provided by sponsor companies that assures customers of product safety, ease of administration and avoidance of misadventure.

Yours sincerely

Katherine Rich
Chief Executive

29th March 2016

MCC Secretary
Medsafe
PO Box 5013
WELLINGTON 6145

Email: committees@moh.govt.nz

Dear Sir / Madam

PROPOSAL TO CHANGE THE CLASSIFICATION STATEMENT WORDING FOR VARIOUS RESTRICTED AND PHARMACY ONLY MEDICINES FROM THE PHARMACEUTICAL SOCIETY OF NEW ZEALAND INC. – REF: 6.5 ON THE MCC AGENDA FOR THE NEXT MEETING

NZSMI (New Zealand Self Medication Industry Association) is pleased to be able to respond to the above public consultation with our submission. We have taken cognisance of the proposal and also the options for consideration with our response below.

NZSMI is the premier body in New Zealand representing companies that are involved in the manufacture, distribution, marketing of consumer healthcare products. We represent approximately 85% of the companies who trade in over the counter (OTC) medicines in New Zealand and specifically 65% of companies in the Complementary Healthcare Product space.

Yours faithfully,

Tim Roper
Executive Director
New Zealand Self-Medication Industry

EXECUTIVE SUMMARY

NZSMI is strongly opposed to the proposal advocated by the Pharmaceutical Society of New Zealand Inc (PSNZ).

Our opposition can be summarised under the various headings of:

1. Safety;
2. Standardisation and uniformity;
3. Traceability;
4. Benefits of advertising OTC products to consumers.

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1. Issue of Safety

When an OTC product is registered for sale in New Zealand, stringent labelling requirements set by Medsafe as the regulator must be adhered to. Only labels approved by Medsafe can be distributed into the marketplace. Detailed information needs to be provided on the pack itself, and also often through pack inserts or consumer information leaflets that provide added information to consumers about the product.

Details such as size of the typeface, colour, the layout of the text, and more importantly dosage and administration and warning statements are all considered to ensure that safe use of the product by consumers is optimised. This level of detail would not be matched by pharmacists providing their own packs from the dispensary, thereby potentially depriving the consumer of a permanent source of information about the product for reference after purchase. It is well-known that information retention is optimised if read, rather than heard, and if it is delivered more than once – good permanent labelling of the product fulfils these criteria. This issue is of particular concern as some of the products proposed are pharmacy only medicines and so could be sold with no intervention by a pharmacist.

There is also a question regarding which CMI a pharmacist would supply if the product was dispensed from a larger prescription pack. It would not be appropriate to supply a CMI for an alternative brand available OTC as the content may be different (eg warnings about excipients, shelf-life & storage recommendations). Similarly it would not be appropriate for the CMI of the prescription product to be provided as this may contain different indications, dosage and warnings. This situation would, therefore, mean patients would not be able to access CMI for products sold under this manner, or pharmacists would need to create these themselves and take liability for the content.

Post market surveillance of OTC and prescription products is a critical part of ensuring customer safety, and this is the responsibility of sponsors of medicines in New Zealand. This proposal would make it very difficult for sponsors to meet these requirements if prescription products were able to be dispensed OTC by pharmacists not in an original pack.

In the event of a product supplied by a pharmacist being inappropriately labelled with all the required information and warnings that are imposed on sponsors of products in New Zealand, the question needs to be asked would the pharmacist be legally liable should misadventure take place because the consumer was not provided with all of the information that was relevant to that particular medicine.

2. Standardisation and uniformity

The value of having Medsafe as the regulator approve a product for release onto the market in New Zealand ensures a high quality of labelling presentation and uniformity. This would not be possible if the proposal as indicated is accepted. There are over 900 pharmacies in New Zealand and without question there would be a variety of practice when preparing and packing and labelling product for sale from the pharmacy as suggested in the proposal. Customers have every right to expect the very highest standard of presentation in both the identification of the product, the warnings and precautions that may well be required to be considered and all other instructions that are deemed as necessary by the regulator.

3. Traceability

In approving a pack for OTC supply, Medsafe as the regulator ensures appropriate batch labelling requirements to maintain accurate traceability in the event of a recall of that particular product. If the supply is allowed as suggested in the PSNZ proposal, recall of that particular pack through identification of batch number from the supplier would be impossible.

Regulation 23 of the Medicines Regulations 1984 provides a list of requirements for the label of a dispensed medicine, but omits to include others which are mandatory for an original pack supplied by a sponsor such as:

- batch and expiry;
- warnings and precautions;
- trade name;
- classification;
- indication; and
- storage conditions.

We believe that these are essential in the supply of any medicine provided over the counter, both from a safety and traceability perspective.

4. Benefits of advertising OTC products to consumers

There is no doubt that advertising of OTC medicines by sponsors in New Zealand provides relevant and important information to consumers in advising them what products are available to treat certain conditions and to prevent other conditions occurring. Advertising assists in notifying consumers as to what products/brands are available, especially if they have switched from prescription to OTC.

Education and health literacy all benefit due to the ability to advertise products to consumers. However, it is also expected that advertising will provide a sales response – under the PSNZ proposal the expected response may be seriously impacted and such an effect would impact sponsor's ability to advertise further. Consequently, consumer medicine education and health literacy could be seriously jeopardised in the event of the proposal being approved.

When a product is switched from prescription only status to either: Pharmacist, pharmacy only or general sales, the Medicines Classification Committee pays serious attention to relevant aspects of the label statement database. In fact the MCC wants to be assured that consumers are very clear with regard to the information provided on the label, the directions regarding how the product should be taken or used, and all warnings and precautions that need to be clear and concise and easily interpreted by the consumer.

NZSMI would argue that the high standard of presentation provided by sponsor companies assures customers of product safety, ease of administration and avoidance of misadventure.

[redacted]

5 April 2016

[redacted]

Ms. A. Kerridge
Secretary – Medicines Classification Committee
Medsafe
Ministry of Health
P. O. Box 5013
WELLINGTON 6145

[redacted]

[redacted]

PROPOSAL TO CHANGE THE CLASSIFICATION STATEMENT WORDING FOR VARIOUS RESTRICTED AND PHARMACY ONLY MEDICINES FROM THE PHARMACEUTICAL SOCIETY OF NEW ZEALAND INC.

REF: 6.5 ON THE MCC AGENDA FOR THE 55th MEETING

[redacted] is strongly opposed to the proposal put forward by the Pharmaceutical Society of New Zealand Inc (PSNZ).

Our opposition broadly falls into the following categories:-

1. Safety
2. Standardisation and uniformity
3. Traceability
4. Benefits of advertising OTC products to consumers

These categories are further discussed on the following pages. [redacted] believes that consumers deserve and should expect to purchase product with high quality labelling, and so we offer the following counter-proposal for the MCC to consider:-

"That all medicines classified as Restricted, Pharmacy Only or General Sales medicines should be sold in the manufacturer's original pack in order to ensure the purchaser receives full and adequate information on the uses, dosage, contraindications, warnings, storage conditions and batch numbering appropriate for the product, unless the classification of the compound expressly allows dispensing of the product over-the-counter from a bulk pack."

Safety

When an OTC product is registered for sale in New Zealand, stringent labelling requirements set by medicines legislation and Medsafe, as the regulator, must be adhered to. Often best-practice guidelines to labelling above and beyond the legal/regulatory requirements are also applied.

Only labels approved by Medsafe can be distributed into the marketplace. These requirements specify detailed information to be provided on the outer pack, thereby assisting the consumer with the purchase decision, and are also often repeated on inner labels. Pack inserts or consumer information leaflets that provide added information to consumers about the product are often required by Medsafe to be included, or are voluntarily provided by sponsors in the interests of informing customers about their products.

Details such as size of the typeface, the layout of the text, and more importantly dosage and administration and warning statements, are all considered by the sponsor and by Medsafe to ensure that safe use of the product by consumers is optimized. This level of detail would not be matched by pharmacists providing their own packs from the dispensary, thereby potentially depriving the consumer of a permanent source of information for the product, especially for reference after purchase. It is well-known that information retention is optimized if read, rather than heard, and if it is delivered more than once – original manufacturer labelling of the product fulfils these criteria, offering a permanent source of information for as long as the consumer has the medicine. This issue is of particular relevance for those products that are pharmacy only medicines, which under the PSNZ proposal could be provided to the consumer without interaction with a pharmacist and with very limited labelling.

Much effort goes into the design and wording of the labels and leaflets of non-prescription medicines. High percentages of populations have said that they always read the label or package insert completely before taking a non-prescription medicine for the first time e.g. 97% in the UK, 91% in Latin America, 83% in Spain (WSMI Advertising of non-prescription medicines to the public). This confirms that the appropriate place for detailed information is labels and leaflets or package inserts, and this is where the consumer expects to find such information. Communicating such detailed information verbally could well be difficult, especially if pharmacy staff are busy and pressed for time, and retention is likely to be poor.

There is also a question regarding what additional written information a pharmacist might supply if a product was dispensed from a larger prescription pack, which a customer might well request. It would not be appropriate to supply the CMI for an alternative brand available OTC as the content may be different (e.g. warnings about excipients, shelf-life, storage recommendations, sponsor). Similarly it would not be appropriate for the CMI of the prescription product being dispensed to be provided, as this may contain different non-OTC

indications, dosages and warnings. It appears patients would not be able to access CMI for products sold under this proposal, or pharmacists would need to create the information themselves and take responsibility for the content.

Post market surveillance of OTC and prescription products is a critical part of ensuring customer safety, and this responsibility belongs to sponsors of medicines in New Zealand. If prescription products are able to be repacked and dispensed over-the-counter within pharmacies, it is an impossible task for sponsors to fulfill their responsibilities in this area. Batch traceability, and even sponsor information, may be lost. Currently, consumers frequently contact the sponsor directly post-purchase (from label information) if more information is required or problems are experienced. This important source of information for sponsors, both to act on and to report, may be lost.

It is forseeable that a product repacked and supplied over-the-counter in a pharmacy could be inappropriately labelled through omission of the required information imposed on sponsors of products in New Zealand, or provision of incorrect information, or other possibilities such as contamination of the product could occur. Should a consumer then suffer misadventure that could have been avoided if the product had not been repacked, the question arises as to who ultimately has responsibility for the medicine? It is our view that once a pharmacist repacks an OTC medicine in the manner proposed by PSNZ, that pharmacist also accepts responsibility for adverse events definitely or possibly related to the repacking.

Standardisation and Uniformity

Having appropriate legislated labelling requirements, and Medsafe as the regulator to enforce these requirements, ensures high quality medicine labelling for over-the-counter medicine consumers. The consumer can be confident that many of the details found on one medicine label will also be found on other medicine labels, educating them in the type of information to expect, and in the case of Pharmacy Only medicines enabling them to appropriately self-select medicines and improve their self-care. This would not be possible if the PSNZ proposal is adopted. There are over 900 pharmacies in New Zealand, and without question there would be a variety of practice when preparing, packing and labelling product for sale from the pharmacy as suggested in the proposal. Customers have every right to expect the very highest standard of presentation in both the identification of the product, the warnings and precautions that need to be considered, and all other instructions that are deemed necessary by the regulator.

Traceability

Medicines labelling regulations ensure appropriate batch labelling requirements to maintain accurate traceability in the event of a recall of that particular product. Supply of repacked product over-the-counter means that recall of a particular batch through identification of

batch number from the supplier would be impossible, unless the pharmacy records and stores appropriately the patient name, address and contact details against the product batch number for all over-the-counter sales. Regulation 23 requires that a unique identifying number or code for the prescription or record of supply by assigned to the medicine – while pharmacists are familiar with this process for prescription and restricted medicines, pharmacy assistants may not be and we are concerned that these requirements may not be met in the case of the Pharmacy Medicines proposed for reclassification as it is not mandatory for the pharmacist to be involved in the sale of these medicines.

Regulation 23 of the Medicines Regulations 1984 provides a list of requirements for the label of a dispensed medicine, but omits to include others which are mandatory for an original pack supplied by a sponsor such as:

- batch and expiry;
- warnings and precautions;
- trade name;
- classification;
- indication; and
- storage conditions.

We believe that these are essential in the supply of any medicine provided over the counter, both from a safety and traceability perspective.

Benefits of Advertising OTC products to Consumers

There is no doubt that advertising of OTC medicines by sponsors in New Zealand provides relevant and important information to consumers, advising them what products are available to treat certain conditions and informing them of such things as when new products become available, or if a product changes, or if there is a new application for the product. Advertising assists in notifying consumers as to what products and competing brands are available, especially if the products have been reclassified from prescription to OTC. It creates awareness, helps consumers search for the products they need and directs consumers to labelling that provides essential details for the safe and appropriate use of the product.

Education and health literacy benefit due to the ability to advertise products to consumers. Public health benefits and the benefits of market competition also accrue (WSMI Advertising of non-prescription medicines to the public). However, the commercial reality is that companies invest in advertising expecting a sales response. Should the PSNZ proposal be adopted the expected response may be seriously impacted, and such an effect would impact sponsor's ability to advertise further. Consequently, consumer medicine education and health literacy could be affected in the event of the proposal being approved.

In addition to the general comments above [redacted] would like to comment on some of the specific proposals made by the PSNZ, as follows:

Lansoprazole

The proposal notes that professional guidelines were made available to pharmacist following the reclassification of omeprazole to Restricted Medicine. These professional guidelines were developed by [redacted] in conjunction with gastroenterology specialists and the School of Pharmacy, and were delivered to pharmacists at considerable cost to [redacted] as part of our commitment to the reclassification of omeprazole. Douglas Pharmaceuticals have chosen not to make lansoprazole available over-the-counter, and as such have not invested in training pharmacists on their product. While the two products are similar, they are not the same and [redacted] believes that product specific training for pharmacists and pharmacy assistants is necessary as new chemicals enter the over-the-counter market. Without the benefit of such training, we believe it is appropriate that currently lansoprazole is relatively unavailable as an OTC medicine.

Furthermore, the proposal that pharmacists could make a trial comparison of lansoprazole over another proton pump inhibitor is not to be encouraged. Such ad hoc, uncontrolled comparison will not add to the body of knowledge of these well-researched medicines, and the inference that pharmacists could inform themselves in this way is not scientific.

Omeprazole and Pantoprazole

The suggestion that pharmacists could test or compare tolerability or efficacy between proton pump inhibitors is of concern for the reasons as stated above. The industry takes clinical trial of any sort very seriously, and such testing and comparison without informed consent and without measured outcomes should not be encouraged.

Furthermore, while not expressly stated, there is a suggestion that should a PPI not be efficacious the proposed reclassification would offer pharmacists the opportunity to provide the customer with a different PPI. While this is true, the treatment guidelines for heartburn (New Zealand Guidelines Group) and the labelling advice for Losec specifically state that lack of symptom resolution should initiate referral to a doctor, and trial of a different PPI would be inappropriate in this case.

Alternative Proposal

When a product is switched from prescription only status to either Pharmacist Only, Pharmacy Only or General Sales, the Medicines Classification Committee pays serious attention to relevant aspects of the label statement database, including consideration of whether the required warnings are adequate for the classification under consideration or if additional warnings should be made. The MCC wants to be assured that consumers receive accurate and complete information from the label. The directions regarding how the product should be taken or used, and all warnings and precautions need to be clear,

concise and easily interpreted by the consumer. The high standard of presentation currently provided by sponsor companies' labelling assures customers of product safety, ease of administration and avoidance of misadventure.

An essential part of reclassification for any product is the proposed labelling – product specific reclassification proposals for MCC consideration must show detailed proposed labelling, both in form and content. A built-in platform of the reclassification process is that consumers can be appropriately informed by the product labelling. Consequently, it is not clear how products might be reclassified in future if there is the possibility that consumers might receive the product not accompanied by the manufacturer's labelling. We submit that in the medium-to-long term adoption of the PSNZ proposal could prove an impediment to reclassification.

[redacted] considers the labelling of its OTC products as the primary method of communicating with consumers. As such, we ask the MCC to consider the proposal that a general rule for all over-the-counter medicines be adopted – that they should be provided in their original manufacturer's packs approved by the Minister or the Director-General for distribution unless the classification expressly permits otherwise. In this way, consumers would be assured of receiving appropriately labelled product most of the time, while those prescription products that can be sold OTC in certain circumstances and for which consumers receive more intensive pharmacist intervention e.g. sildenafil, or OTC products where there is no commercially available presentation e.g.trimethoprim, could still be made available.

Yours sincerely

Advertising of nonprescription medicines to the public

A significant contributor to healthcare

WSMI

WORLD *self*-MEDICATION INDUSTRY

Advertising of nonprescription medicines to the public

Contents

Executive summary

Advertising creates awareness of nonprescription medicines, helps consumers in the search for products they need, and directs consumers to labeling that supplies details essential for safe and appropriate product use. Nonprescription (or over-the-counter, OTC) medicines are medicines which are approved as safe and effective for use without a doctor's prescription. These and other self-care products are available without medical supervision and can be purchased by patients and consumers through pharmacies and, in many countries, from supermarkets or other retail outlets. As no health-care professional is necessarily involved in their use, advertising directly to the public of the availability of nonprescription medicines is essential and makes an important contribution to public health.

Advertising is suited to the transmission of simple, focused messages. Information on nonprescription medicines for patients and consumers comes in various forms and from various sources, including advertising and labeling, advice from pharmacists or other health professionals, the internet, and so on. Each of these information sources contributes in different ways to a patient's knowledge and understanding.

Advertising has a general role to play in modern healthcare, ranging from publicly-funded communication programs encouraging better health practices to industry communication programs describing the availability of nonprescription medicines in support of better health.

The emergence of chronic diseases such as cardiovascular disease, cancer and diabetes as the main future source of morbidity and mortality in most countries is also particularly significant. These are diseases which are caused by factors substantially within an individual's control — tobacco smoking, insufficient physical exercise and excess body weight for example. Government health promotion campaigns helps people to think more about their health and become more aware of their symptoms and condition. Nonprescription medicines' advertising reinforces this by showing the availability of medicines that can help.

Regulations should recognize the role, and limitation, of advertising. Basic standards will ensure that the information conveyed is truthful and not

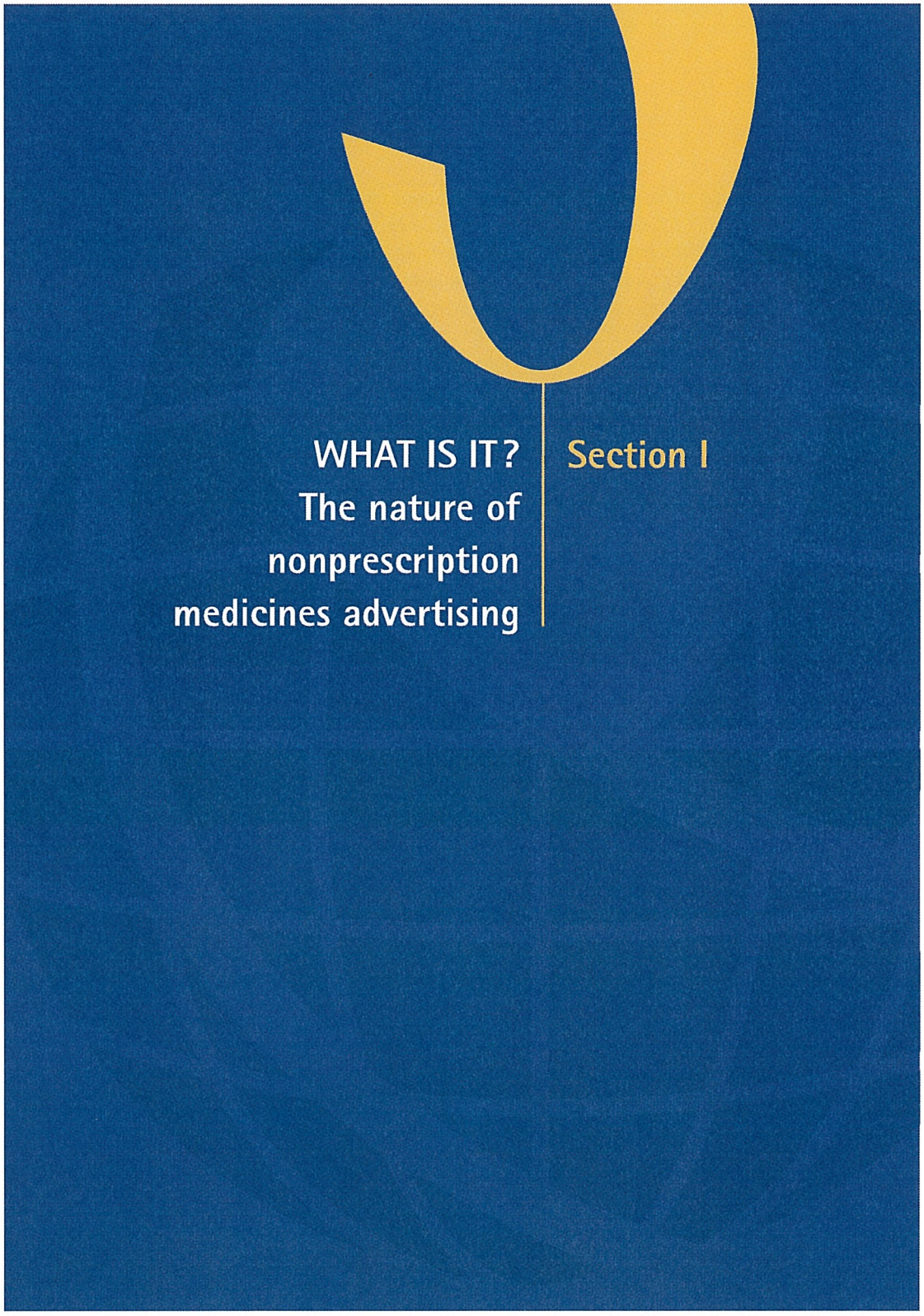
misleading to consumers. Health departments, regulators and manufacturers should work together to ensure that consumers have the information they need about the benefits and risks of the medicine. A mix of government and self-regulatory tools that help ensure industry responsibility and accountability can be used effectively to oversee advertising. Nonprescription medicines manufacturers are committed to strict codes of practice, both as individual companies and through membership of country trade associations.

This monograph summarises the case for clear, ethical and efficient advertising of nonprescription medicines, recognizing its limitations but also demonstrating its special role in the new global public health context.

Scope of the monograph

The scope of this monograph is all self-care products available without a medical prescription. This includes herbal products and supplements, as well as nonprescription medicines or OTCs. Advertisements for all self-care products should be truthful and not misleading to consumers, and treated equally in the regulatory control processes for their advertisement.

It must also be emphasized that this monograph does not address the entirely separate issue of advertising of prescription drugs. The fundamental difference between prescription medicines and self-care products is that the latter can be purchased and used by the consumer of the medicine without the necessary intervention of a medical doctor. This has far-reaching consequences for supporting the appropriate use of nonprescription products by consumers and patients. Informing individuals about 'responsible' self-medication is appropriate; entirely different controls are necessary than those on doctor prescribing of prescription medicines. For self-care products there is therefore a special place for the provision of consumer information, and in making patients aware of product choices. For self-care products, labels, leaflets and, not least, consumer advertising have a special importance.


WHAT IS IT?
The nature of
nonprescription
medicines advertising
Section I

The extent and purpose of advertising

Advertising materials which are aimed at consumers and those persons who may legitimately purchase medicines on behalf of another consumer (e.g. parents, who purchase medicines on behalf of their children) can come in a variety of forms, including :

1 Printed advertising material (e.g. newspapers, magazines, booklets, posters, direct mail materials etc.);

2 Electronic media advertising, such as websites, press releases intended for internet publication, and other on-line advertisements;

3 Audio and audiovisual advertising (e.g. cinema, television or radio commercial, videos);

4 'Other' – for example promotional scripts for use by telephone help lines, promotional text messages, aerial promotions such as hot air balloons, outdoor advertising, and so on.

Consumer-directed advertising has one principal purpose : "to alert consumers to the availability of products for conditions suitable for self-medication" (WSMI, 1999). To accomplish this, advertising must attract attention, stimulate interest and provide information to mass audiences of consumers about what a particular product might do. The focus is on informing consumers about the indications suited to self-care and the products available.

Overall, consumer-directed nonprescription medicines advertising can achieve a number of purposes. It can :

- increase awareness among patients and consumers about their condition and about the availability of suitable medicines for self treatment;
- alert consumers to new products and new indications and reinforces other forms of communication about a product and brand;
- develop brand recognition to provide the consumer with confidence in the brand and the company;
- facilitate product search and helps consumer make informed selections

- stimulate competition in the areas of product quality, product improvement and product development;
- help bring market forces into play, creating competitive product prices;
- reinforce good medicines use ("always read the label;" "if symptoms persist, consult a healthcare professional").

Without advertising, consumers would be at a disadvantage. They would have less information on which to base their search for and selection of self-care health products.

The limitations of advertising

Advertising is a low involvement medium ill-suited and demonstrably ineffective for carrying detailed or highly specific information. Rather, detailed information is more relevant at a time a product is selected for purchase, and later when the product is used. This more detailed information can come from discussion with a healthcare professional and in particular in the case of nonprescription medicines, from the product label and leaflet.

Thus advertising alone cannot convey all of the information that a patient needs to practice responsible self-medication. Advertising is limited in how much information can be conveyed. It is well-known that the greater the volume of information in an advertisement, the smaller the likelihood of a particular item being remembered (box 1). Recognizing its limitations, advertising must then be reasonably focused on what it can do: attract the viewer, listener, or reader's attention.

Summarizing a report by the International Advertising Association, the World Health Organization describes the purpose of advertising as: "Attract attention, offer choices, and provide limited general information to mass audiences of consumers. It must stimulate the interest of prospective buyers in a... product [and] inform them of what it may do for them... Therefore, advertising should not be overloaded with information to the point that the individual prospective buyer may fail to comprehend it or may even ignore it."

Box 1 Consumers recall fewer than 3 messages from an advertisement

A major study in Britain by Taylor Nelson Research (1990) found that consumers usually recall fewer than 3 messages from an advertisement. Those in the study who viewed television commercials containing the full label text from a nonprescription medicine could not remember the details. In addition, detailed information significantly decreased recall of the main messages concerning the medicine's name and purpose. Viewers of full-text commercials were more likely to describe them as 'confusing', 'complicated', 'unclear' and 'having too much information'.

A consistent study in Germany (Kepplinger, 1990) showed that specific items of information in print advertisements are less likely to be remembered as the volume of information in the advertisement increases. The potential effectiveness of information is "inversely proportional to the amount of information presented". The study concluded that putting a lot of detailed information about contraindications and side effects into an advertisement has no substantial effect on consumer knowledge, even when such information is repeated. By contrast, the information on medicines labels does increase the knowledge of a large proportion of consumers, and reinforcement by health professionals such as pharmacists can also be very valuable.

Consistent with these results, it has been demonstrated specifically that the addition of warning messages to advertisements will not necessarily lead to increased compliance with label directions among consumers (Stewart and Martin, 1994)

In summary, detailed information about product use and risks decreases recall of the main messages in the advertisement. Advertising is especially suited to raise the awareness of patients and consumers on a particular public health concern or disease, or to communicate the availability of a medicine, but it cannot alone provide comprehensive instructions.

General messages in advertisements

Because an advertisement is not the appropriate place for detailed information, a general invitation to read carefully the instructions accompanying the medicine is more useful for conveying use information and any cautions.

In 1992, the European Union decided to free advertising of nonprescription medicines from including detailed information. In preference the EU developed a directive on medicine information on leaflets and labels which has to be written in consumer language and where appropriate should be tested with consumers to establish that it is readable and understandable. The European advertising directive requires references in advertising to the label and leaflet information to encourage consumers to read them. When appropriate, consumers could also be invited to discuss with a health professional for additional information and appropriate advice (for example in cases where a symptom persists, suggesting a more serious underlying condition).

Some examples of messages that have been adopted by some countries are:

- Portugal: "Read the information on the label or in the leaflet."
- Poland: "Read carefully the instructions on the package leaflet or on the outer packaging."
- Argentina & Australia: "Read the instructions for use carefully and consult a doctor in case of doubt."
- Brazil: "Ask for medical advice if symptoms do not disappear."
- Canada: "This product may not be right for you. Always read and follow the label."

Label and leaflet information

There are more effective communications means than advertisements to convey fuller information to consumers. Labels and leaflets are especially important in the nonprescription sector although these can still be supplemented by advice from pharmacists or other health professionals when needed. The role of the label is to allow consumers:

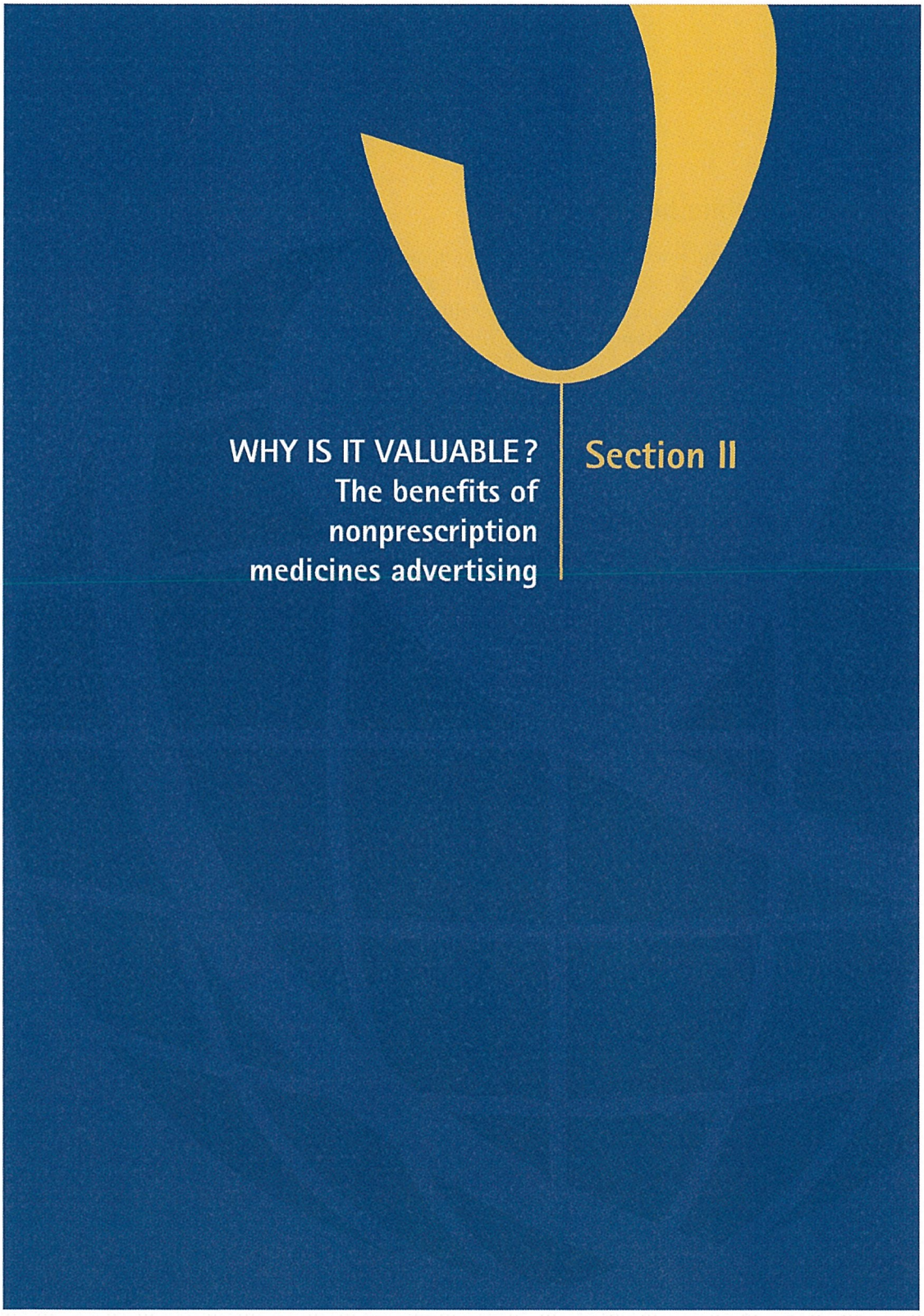
- to quickly and easily make a choice about the appropriateness of this medicine for their needs, at the point of sale;
- to find and appropriately use instructions for using the medicine safely and effectively, at the point of use;
- to access further information, if they want to know more about the medicine, at any point.

Consumer behaviors should be taken into account when elaborating the wording to be placed on advertisements or outer packaging of products. Much effort goes into the design and wording of the labels and leaflets of nonprescription medicines. High percentages of populations have said that they always read the label or package insert completely before taking a nonprescription medicine for the first time: from 97% in the UK through 91% in Latin America to 83% only in Spain. This confirms that the place for detailed information is in labels and leaflets or package inserts, not in advertisements.

Conclusion of Section I

The specific objective of advertising is to alert the public to their condition and the availability of personal treatments. Because advertising of consumer products is limited by the amount of information that can be conveyed, its role resides simply in attracting attention and raising awareness. Other communication channels such as product labels and leaflets are more important for presenting larger amounts of detailed information.

Advertising of nonprescription medicines has a number of positive benefits for public health in general, the marketplace, and the individual patient.


WHY IS IT VALUABLE?
The benefits of
nonprescription
medicines advertising
Section II

Public health benefits

Advertising is well-suited and efficient in raising awareness on health matters; research carried out on the effects of direct-to-consumer advertising of prescription drugs suggest that health advertisements motivate people to seek out more information about either a drug or their own condition.

Advertising of nonprescription medicines can play a similar role in public awareness. By addressing the public's instinct for taking care of themselves, nonprescription medicine advertisements can in some circumstances reinforce a public health awareness prevention or self-care program (Box 2).

Box 2 The role of advertising in public health – the example of smoking cessation

In estimating the impact of allowing nonprescription sales of nicotine replacement therapy (NRT) in the United-States on increasing the numbers of smokers quitting, Shiffman et al (1997) found:

"The ability to sustain smokers' interest in quitting with NRT may be attributable, in part, to the intensive advertising and promotional campaigns that have characterized the OTC market in NRT....Although many promotional activities promote particular products, this marketing and outreach effort also brings smoking cessation messages before the public in unparalleled intensity. This makes it particularly plausible that many of the quit efforts involving OTC NRTs are incremental efforts that would not otherwise have occurred.... The middle-ground estimates of approximately 225 000 incremental quits – an increase of almost 20% – are probably quite realistic."

Advertising may also have a positive effect on compliance: Wosinska (2005) reported for prescription drugs that "patients that started a medicine following...advertising are found to be more compliant possibly because they initiate the process and thus are more motivated to continue their therapy".

A different but no less important public health benefit of nonprescription medicines advertising is in encouraging people to look after themselves

when they can and should do so, and not simply go to the doctor on every occasion. Many surveys have shown how much time is wasted by doctors in general practice treating patients with common illnesses that could have been self-managed. Relieving doctors from unnecessary involvement in patient self-care allows them to focus on other priorities, to the general benefit of public health. Advertising of nonprescription medicines may thereby assist in supporting the proper contribution of self-medication to a country's healthcare system.

In summary it is clear that expenditure on nonprescription medicines advertising is a hidden asset of the healthcare system and makes an important (but largely unappreciated) contribution to public health objectives.

Benefits of market competition

Positive and informed consumer behavior is the foundation for a dynamic and well-functioning marketplace. In response, manufacturers compete to provide new, better and different choices for consumers. Manufacturers focus on the development of brands and the freedom to advertise those brands is a key requirement for investment in their development. The resulting dynamic, competitive market delivers consumer choice and helps keep prices down.

Advertising is thus an effective structural tool of an efficient and effective market economy. It brings market forces into play, feeding competition between companies, leading to more medicines being made available, and to improvement in brands, giving as a direct result more choice for patients and consumers.

Brands have a particular significance to the nonprescription medicines sector since it is always a brand that is the object of the advertising[1]– generic manufacturers rarely advertise generic names.

1 A brand is a collection of images and ideas – the name (product and company), a trademark or logo, a slogan, a design scheme, etc. Companies seek to differentiate their brands by brand name, colour scheme, trademark, packaging, shape, company name, intangibles, after sales service etc. The use of the same brand name or trademark for prescription and nonprescription products also helps with consumer confidence when a medicine is switched from prescription to nonprescription use.

Brands began (in the 19th century and before) as a form of consumer protection. This remains true today, with the brand being a statement by the company of its offering, its guarantee, to customers.
Companies invest in developing brands; in the nonprescription sector not only through new products but also through product developments such as improvements in taste, ease of use, clearer patient information, improved formulation, novel presentations, packaging technology, novel administration forms and child-friendly & child-proof technology. For these reasons consumers trust a brand and may therefore be more willing to try new products, encouraging appropriate use of relevant medicines.

In brief, with brands, companies will invest in disease area and brand development. This can benefit patients by:

- increasing choice, and increasing choice widens access;
- raising patient's awareness of their condition and their treatment options;
- improving understanding of how to use the medicine;
- providing guarantees of efficacy and safety;
- providing guarantees of quality, reliability and consistency;
- helping with recognition where there is a multiplicity of choice.

With a branded medicine, and the freedom to advertise, the brand owner has interest in improving medicines, guaranteeing medicine quality, and promoting healthy practices. Without brands, or without the freedom to advertise, the government has to take greater responsibility guaranteeing public drug quality, improving medicines, and for educating patients and consumers in healthy practices such as their possible need for treatment and appropriate use of a medicine.

Advertising does not promote inappropriate consumption

Advertising alerts consumers to the availability of medicines suitable for self-care and self-medication, but it is not the prime factor affecting the consumer's choice of product. For example, television advertising appears to have a limited impact with respect to overall nonprescription medicine use: in Brazil (1997), 81% of consumers disagreed with the statement: "I customarily purchase medicines advertised on TV".
In Italy, between 1977 and 1987 – a period known in Europe for its large increase in television advertising and in the use of healthcare services, the use of nonprescription medicines increased by only 2%.

Similar results may be found across Europe. Quaeyhagens (1990) gathered data on consumer advertising in the print and electronic media in seven European countries. Total advertising expenditures and sales figures were analyzed for three markets: pain relievers, laxatives and cough and cold remedies, together constituting more than 55% of the overall nonprescription market. Over a five-year period, no correlation was found between overall advertising expenditures, and overall sales. In fact, the French analgesic market showed a reverse trend for advertising and sales. The study concluded that increasing advertising expenditures does not result in a growth in overall consumption, and that effective advertising can only increase the market share of one brand at the expense of another.

The underlying reasons for this are clear. Nonprescription medicines are not "aspirational" goods – people do not choose to buy medicines if they have no need for them. Advertising cannot force people to buy and use a medicine they do not want or need. Thus it is generally accepted that consumer behaviour with respect to the purchase and use of medicines differs greatly from other common items of commerce. For example, clothing and even automobiles are often influenced not by need but by want or desire. They can be impulse items even when very large sums of money are involved.

Self-care health problems on the other hand are clearly dealt with differently by consumers. Nonprescription medicines in particular are not impulse purchase items as the need for a medicine is identified always by the pre-

existence of a health concern. When faced with such a concern, there is a clear search process used by consumers that is different from other common items of commerce. In the first step of the decision process, the consumer experiences the symptoms of an illness, evaluates them and decides whether or not to treat them. Next they activate a search process that depends upon their experience with this condition in the past. Where they have had the condition before, they usually can move directly into the product selection process. Where they have had no previous experience they begin a search for information on available treatment options. The resources for this search are numerous and typically consumers avail themselves of several sources including doctors, pharmacists and the Internet. Medicine advertising plays a role in awareness of products suited for treating health conditions. Either through recall of advertising seen when no problem existed (lowest likelihood of recall) or advertising seen at the time a need is identified, the consumer can add this information to the search process. If a medicine for the specific condition is recalled, the next step is to select a product from the retail environment. Studies show that for first time experiences with self-treatable illness, the consumer will typically go to a pharmacy and seek further information either through the advice of a pharmacist or by comparing medicine labels. When the consumer has a recurrence of a particular condition often they will go straight to product selection and then either choose a medicine that has worked for them before or seek a different product if they are not satisfied with their former selection.

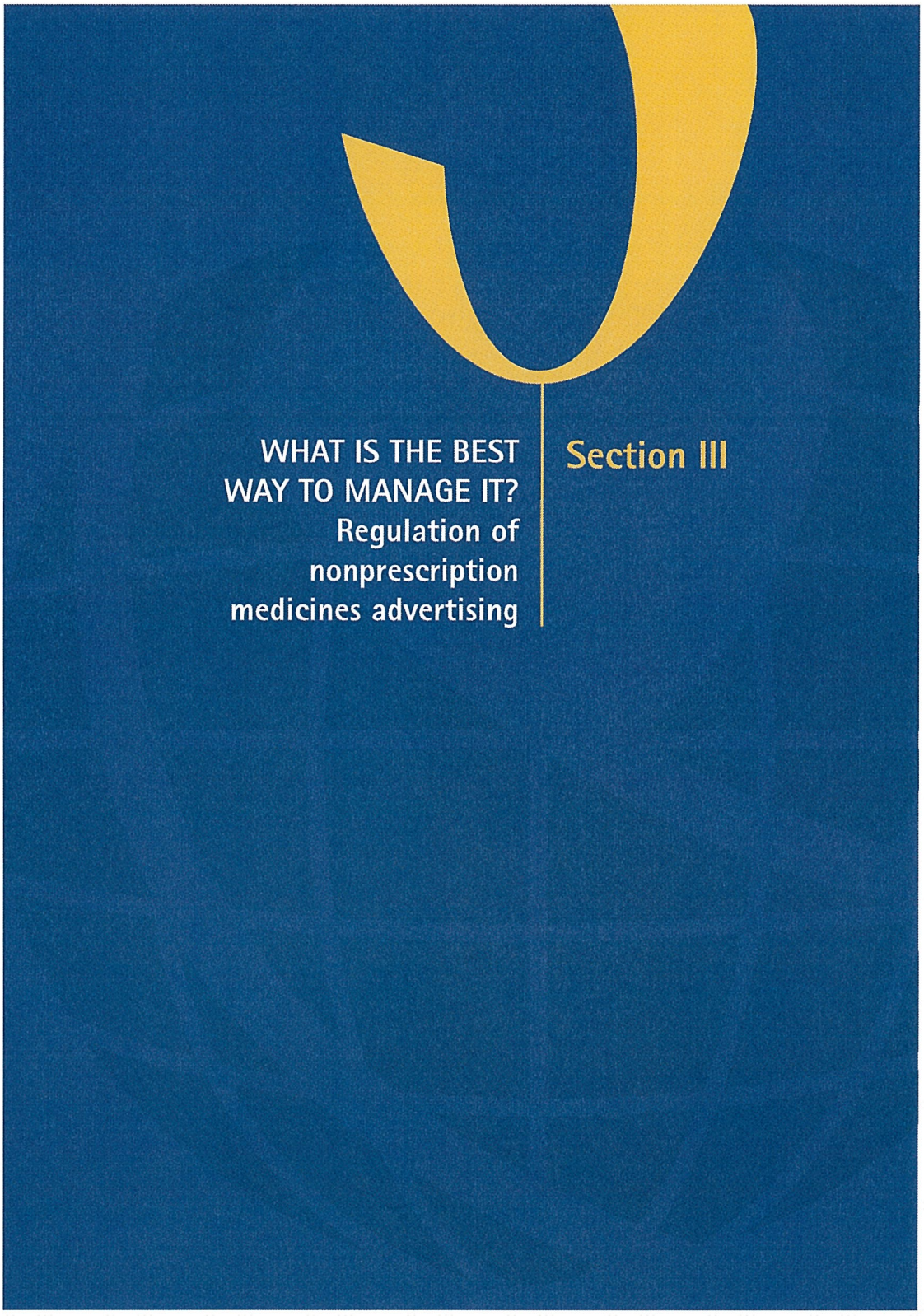
While there is more to consumer health behaviour than outlined here, it is clear that when it comes to nonprescription health products consumers do treat them differently than other consumer goods. To put it plainly, even if a consumer doesn't need a new pair of designer jeans they may still buy them. But if they don't have athlete's foot there is no amount of advertising that will get them to buy an antifungal medicine.

As advertising of nonprescription medicines is not a general consumption incentive, the manufacturer's purpose in advertising their brands is worth understanding. The answer is that manufacturers are competing with each other in a 'zero-sum game' to encourage patients and consumers to use their product, rather than a competitor's. This is one reason the market of the nonprescription medicines sector has grown so slowly for many years

because there is competition between products for market share, rather than growth in overall market size.

Conclusion of Section II

Advertising facilitates the rational use of nonprescription medicines for the benefit of public health, and in this way represents a hidden asset in healthcare. Advertising of nonprescription medicine brands stimulates competition in the area of medicines quality, product improvement and product development, and helps keep prices down. Research shows that advertising of nonprescription medicines does not lead to growth in consumption.



WHAT IS THE BEST WAY TO MANAGE IT? Regulation of nonprescription medicines advertising

Section III

Background

Nonprescription medicines are especially designed and labeled for use without medical supervision, and are approved as safe and effective for such use. There would be little point in approving a medicine for nonprescription use, and then preventing or unnecessarily restricting the advertising of the product. This is not to say that there should be no regulation – indeed high standards should be applied as described in this section – but the underlying approach should be supportive to advertising rather than restrictive.

Advertising of nonprescription medicines is allowed in most countries. The 2002 report of the European G10 Medicines Group illustrates a common government view: "Industry has a legitimate right to advertise products that are available over-the-counter to the public just as the public has a legitimate expectation to know about nonprescription medicines that are available to treat illnesses. There should be no restrictions on advertising of nonprescription medicines, which are not reimbursed, in line with existing requirements for advertising to encourage the rational use of the product and not to be misleading".

General ethical criteria for nonprescription medicine advertising

The ethical criteria for drug promotion which are particularly relevant for self-medication products are highlighted in WHO's Regulatory Assessment of Medicinal Products for use in Self-Medication (2000):

- "While advertisements to the general public should take account of people's legitimate desire for information regarding their health, they should not take undue advantage of people's concern for their health".
- "While health education aimed at children is highly desirable, drug advertisements should not be directed at children".
- "Advertisements may claim that a drug can cure, prevent, or relieve an ailment only if this can be substantiated."
- "They should also indicate, where applicable, appropriate limitations to the use of drugs".

- "When lay language is used, the information should be consistent with the approved scientific data sheet or other legally determined scientific basis for approval. Language which brings about fear or distress should not be used".

In short, advertising should contain only approved indications, it should not be directed to children, and it should not create fear or apprehension. Basic standards of advertising should ensure that the information conveyed is truthful and not misleading to consumers.

Mechanisms for regulation of advertising of nonprescription medicines

Different mechanisms can be used to ensure that nonprescription medicine advertisements are truthful and not misleading to consumers. Two dimensions are of importance. Firstly, whether a pre-release or post-publication system for advertisements is in place. For a pre-release system, advertisements are formally approved before they are released to the public. A post-publication system relies on a complaints procedure being applied after the event. The second dimension is who undertakes the task of applying the regulatory process – a government or independent body, industry, or some combination of each of the interested parties. Of course even systems that rely solely on industry oversight procedures will usually have some government oversight or monitoring process remaining in place.

Systems where the government has a strict pre-control over advertising are gradually disappearing because they tend to impair the efficiency and effectiveness of advertising in its role of stimulator of the market competition. Substantial delays meant higher operating costs for the companies and also imposed an unnecessary workload on regulatory agencies' staff. It is also difficult for government authorities to assess and judge proposed advertisements with technical consistency. The global trend is now towards self-regulatory or co-regulatory methods with government post-publication surveillance (i.e., taking action against violations rather than pre-clearing the advertisements).

In practice national laws, voluntary industry codes on a national level, and responsible individual company action are effective in maintaining high standards of advertising.

Pre- or post-publication approval

A pre-clearance system for advertisements is carried out before they can be released. The pre-clearance may be carried out by the government, by the industry or by independent bodies. The pre-clearance may be required by the Law, or may be an industry voluntary procedure, as part of their codes of practice. For cultural and historical reasons different, but equally effective, approaches have evolved in different countries regarding pre- and post-publication controls on nonprescription medicines advertising.

In Australia, it is a legal requirement that all advertisements for therapeutic goods directed to consumers, published or broadcast in mainstream (designated) media must be approved before publication or broadcast. The Ministry for Health and Ageing has the responsibility for approving advertisements, but the responsibility has been delegated to industry trade associations (the Australia Self-Medication Industry, ASMI and Complementary Healthcare Council, CHC) as part of a co-regulatory arrangement.

In the USA, the approval of the advertising material is given prior to publication by the major broadcast TV networks who have legal clearance departments.

In Canada, drug advertisements are reviewed and pre-cleared by Independent Agencies. Consumer-directed advertising for self-care products are pre-cleared by Advertising Standards Canada (ASC) and Broadcast Clearance Advisory (BCA).

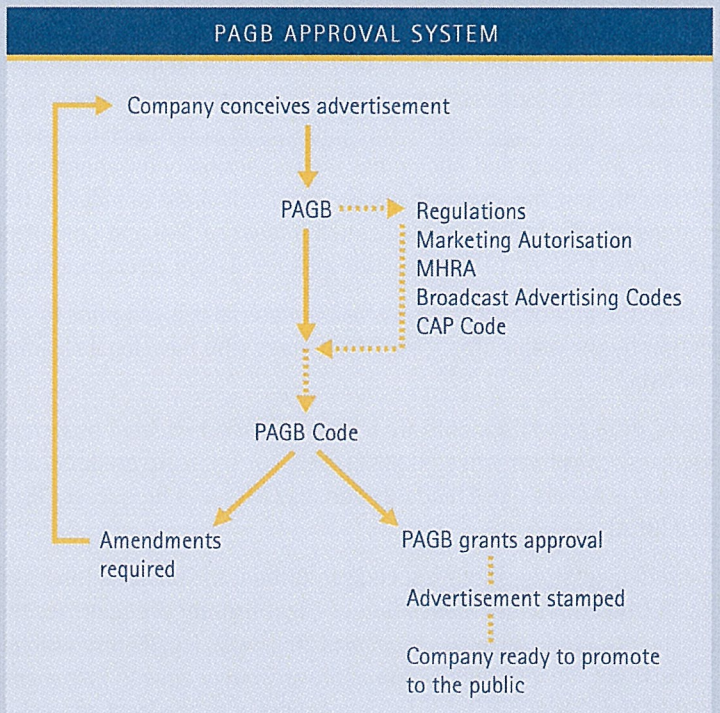
In some self-regulatory systems, such as in Britain, the manufacturer association PAGB (the Proprietary Association of Great Britain) pre-approves the advertisements. While member companies are always legally responsible for their advertising, the pre-publication approval system aims to help members ensure that their consumer advertising complies with the legal and voluntary requirements. The review process usually also involves representatives of the advertising industry and others (Box 4).

Box 4 The pre-approval system of advertising material in Britain

3.4.1 PAGB's pre-publication approval of advertising materials has helped members achieve a high level of compliance with both statutory and self-regulatory requirements.

3.4.2 Specialist staff carry out the pre-publication approval of advertising materials. PAGB has access to independent medical and legal expertise to advise on evidence and matters of interpretation under the PAGB Consumer Code.

3.4.3 The system of pre-publication approval is as follows:



- the member company, or agents working on behalf of the member company, conceive the advertising.
- the member company, or agents working on behalf of the member company, submit the advertising to PAGB for approval.
- PAGB checks the advertisement against the rules in the PAGB Consumer Code, the Marketing Authorisation and any other regulation or code of practice which applies to the specific medium for which the advertisement is intended. Any queries over medical or legal claims are referred to PAGB's medical and/or legal advisers.
- PAGB notifies the member company or agents working on behalf of the member company of any changes required, or evidence which is needed, before the advertisement can be approved.
- once PAGB is satisfied that the advertisement complies with the PAGB Consumer Code, it is approved, subject to 'PAGB's Terms of Approval for Advertising' and the company is notified.
- the advertisement can now be seen by the public.

Source: PAGB's advertising codes, summary version, page 7:
http://www.pagb.co.uk/pagb/downloads/advertisingregulations/PAGB%20Summary%20Medicines%20Advertising%20Codes.pdf

Mexico is an example of a post-publication control system. Since April 2003, members of AFAMELA, the self-care trade association, have been exempted from pre-clearance of advertising. This agreement with the Mexican Regulatory Agency (COFEPRIS) was based on the principle that, by adhering to AFAMELA, members comply with the association's Codes which were found by COFEPRIS to exceed the requirements expressed in the legal provisions. Other country examples of post-event surveillance are Argentina, Germany, Japan, Croatia and the USA.

Post-event controls & complaints procedures

Whichever system is in place, there is always in addition a post-publication oversight of the advertising. Companies are in competition and are the first to point out and complain about a competitor should an unethical, misleading or unfair advertisement be broadcast to the public. Complaints by consumers and health professionals also play a role in making these systems work. There are also government post-controls, as well as independent Advertising Standards Authorities which carry out surveys separate from complaints.

In Europe, article 97 of the Community Code states that "member states shall ensure that there are adequate and effective methods to monitor the advertising of medicinal products. Such methods shall in any event include legal provisions under which persons or organizations regarded under national law as having a legitimate interest in prohibiting any advertisement inconsistent with this Directive may take legal action against such advertisement, or bring such advertisement before an administrative authority competent either to decide on complaints or to initiate appropriate legal proceedings".

In the USA, the Federal Trade Commission (FTC) controls the advertisements after their publication. In addition, the Council of Better Business Bureau, National Advertising Division, runs a non-governmental advertising complaint system which reviews advertising complaints from consumers, competitors, or on its own initiative. Germany, Japan and Mexico are other examples of industry self-regulation with government post-publication controls and ample enforcement tools against violative advertisements. In fact, most industry self-regulated systems have governmental post-controls of advertising. However, experience has shown that punishments against violations of advertising rules are usually not needed in a self- or co-regulatory system.

Nevertheless, penalties for breaching advertising laws and / or self-regulatory codes can be substantial and include: discontinuation of the advertisement, circulation of a retraction statement, imposition of fines (high enough to be discouraging), formal publication of the decision, referral to the Ministry of Health, withdrawal of association membership, withdrawal

of right to advertise, and withdrawal of marketing authority for the product.

Industry self-regulation works well for a number of reasons, not simply because the penalties for transgression are substantial. Companies know that the alternative - direct government control - is undesirable, being slower and more costly.

Self-regulatory systems of advertising control

Self-regulation in the nonprescription medicine industry is the voluntary use of agreed Codes of Practice by pharmaceutical companies regarding promotion and advertising of medicines to the public. These codes are written and adopted by national associations of nonprescription medicine and self-care manufacturers. Codes contain procedures for judging complaints along with measures for non-compliance. Self-regulation works because companies in competition with each other are likely to be the most expert and sensitive critics of their competitor's advertising.

In some cases the Self-Regulatory Codes are underpinned by the law. This is then called Co-Regulation as both the government and the industry share the role, with the industry sometimes doing the pre-clearance.

Britain's positive experience with a self-regulatory system (described in Box 4) is reflected in the European Legislation which recognizes "the role of voluntary control of advertising of medicinal preparations by self regulatory bodies and recourse to such bodies" (Article 97, Paragraph 5 of Directive 2001/83/EC).

In Japan, a voluntary Code of Advertising Practice was issued in 1955 jointly by the Federation of Pharmaceutical Manufacturers Associations (FPMAJ) and the Japan Self-Medication Industry (JSMI). The code voluntarily subscribes to the content and spirit of both the Japanese Pharmaceutical Affairs Law and the 'Standards for Appropriate Advertisements of Pharmaceuticals' as edited by MHLW, the Japanese Health Ministry. The industry voluntary code has been adopted as the tool of reference by the regulatory authorities in view of its "comprehensiveness and reliability".

Many other countries around the world have written and adopted voluntary Codes of Practice. Argentina, Australia, Austria, Brazil, Canada, Croatia, Denmark, the Czech Republic, Finland, Ireland, Poland, Portugal, the Russian Federation, the Slovak Republic, Slovenia, Sweden, Switzerland, the USA are some examples. The positive experiences in self-regulation in Mexico are summarized in Box 5.

Box 5 Self-regulatory systems with government post-controls work well. The example of Mexico.

From April 2003, COFEPRIS, the Mexican regulatory agency (Comisión Federal Para la Protección Contra Riesgos Sanitarios) signed with AFAMELA, the Mexican self-care industry association, an agreement according to which members of the Association are exempted from the pre-clearance of their advertisements. This agreement was based on the understanding that companies comply with AFAMELA's Codes of Ethics. These Codes of Ethics were found by COFEPRIS to exceed the requirements expressed in the agency's Regulation of Advertising.
Controls may be carried out by COFEPRIS after the publication of the advertisements. Violators of the Code and/or Regulation would have to pay a fine and the advertisement would be subject to modification or withdrawal.
Because COFEPRIS has found the system to be working well, it decided in 2005 to extend the system to other healthcare products such as medical devices, diagnostics, and others.

A positive side effect of the implementation of the post-publication control system in Mexico has been a clear reduction of the regulatory agency's workload. And a growing number of healthcare companies are henceforth more responsive to the market, with their advertisements complying with the highest ethical standards of advertising practices.

Conclusion of Section III

Different mechanisms can be used to ensure that nonprescription medicine advertisements are truthful and not misleading. Two dimensions are of importance. Firstly, whether a pre-release or post-publication system for advertisements is in place. For a pre-release system, advertisements are formally approved before they are released to the public. A post-publication system relies on a complaints procedure being applied after the event. Either approach can work well depending upon individual country conditions. Experience also shows that the system of self-regulation works well. There are relatively few complaints and even fewer are upheld by the various bodies reviewing them, both governmental and non-governmental. The strengths of self-regulation are its efficiency and effectiveness when the structure exists to oversee it adequately. It does not use government resource which can be better deployed elsewhere, and it is much faster than government pre-control. This is very important for industry as advertising is frequently season-related. It also reinforces a responsible attitude on the part of companies. In a number of developing countries self-regulatory schemes are being developed with the authorities.

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WSMI

WORLD *self*-MEDICATION INDUSTRY

Memo

Date:	5 April 2016	
To:	Stewart Jessamine, Chair Medicines Classification Committee	
From:	Sarah Reader on behalf of the Ministry of Health	
Subject:	Reclassification of Naloxone	
For your:	Information	

Summary

This memo is to advise you on the Ministry of Health's position on the proposed reclassification of naloxone. The Ministry agrees in principle with the aspiration to make naloxone more widely available. We do not consider that reclassification will, in itself, achieve this goal. However, we consider that reclassification may still be appropriate, enabling pharmacists to supply the medicine accompanied by other relevant information.

Background

The Medicines Classification Committee (MCC) will consider creating a new classification of naloxone as a restricted medicine when used for the treatment of opioid overdose, to harmonise with the Australian Schedule.

Health Canada has also recently down scheduled naloxone when sold for emergency use. Health Canada considered the risk of the administration of an injection by a lay person and decided that the benefit of use in opioid overdose outweighed this risk.

Naloxone

Naloxone is an opioid antagonist – a drug which reverses opioid overdoses. It is highly effective if taken before a person progresses to cardiac arrest, and once administered, begins to take effect within minutes. Adverse effects are very rare but can occur.

Current availability of naloxone

Naloxone is a prescription only medicine, which can be obtained via Practitioner Supply Order (PSO). A PSO allows medical practitioners to administer it without needing to obtain individual prescriptions for each patient. Naloxone is PHARMAC-funded only if obtained through a PSO.

Currently, there are two approved medicines containing naloxone indicated for the treatment of opioid overdose. These are both injectable solutions of naloxone hydrochloride.

Naloxone is carried by hospitals and ambulances, although not all ambulance staff can administer it. Members of the public can also obtain naloxone from their GP via the PSO mechanism, or from pharmacies with a prescription.

Naloxone is also a component in two approved oral dose forms. However, these medicines will not be affected by the reclassification because the naloxone is in combination with another prescription medicine and neither of the medicines are indicated for the treatment of opioid overdose.

Increasing access to naloxone

The Ministry is aware of calls to increase the availability of naloxone in order to reduce opioid overdose following a report published by the Drug Foundation (https://www.drugfoundation.org.nz/sites/default/files/nzdrug-emergency-overdose-prevention-background-May15.pdf).

Opioid overdose is a major cause of harm in New Zealand with 37 reported deaths per year. It is thought that there is under reporting of harm arising from opioid overdose especially from those who are using opioids illegally. Opioids are widely prescribed for pain management and the licit and illicit use is increasing. The Drug Foundation has called for a reclassification of naloxone to allow unrestricted distribution to ambulances and paramedics and retail sale through pharmacies.

Although members of the public can theoretically obtain naloxone through a prescription from their doctor, Ministry data indicates that all naloxone dispensed in New Zealand is provided to medical practitioners through PSOs.

Ministry of Health position

The Ministry is generally supportive of initiatives to make naloxone available.

- We strongly support increased access to naloxone to enable first-responders to treat an opioid overdose.
- We consider that there is merit in exploring other mechanisms for enabling the public to have naloxone on hand to enable quicker administration without having to wait for an ambulance to arrive.

The Ministry does not consider that sufficient consideration has been given to the best and most cost effective methods to achieve these goals. We do not believe that reclassification alone is likely to have a significant impact on increasing availability. In particular we note:

- GPs can already dispense and prescribe naloxone, but the level of activity in this area is low (numbers). There may be merit in investigating whether it would be possible encourage greater uptake of the existing GP dispensing mechanism, including the fact that the PSO instrument can be utilised alongside a standing order to enable other health professionals to be able to administer the medicine.
- PHARMAC does not currently fund naloxone as a prescription medicine obtained from a pharmacy and does not fund restricted medicines without a prescription. Cost is therefore likely to continue make the product inaccessible to the target population.
- Restricted medicine supply is intended for use by a given individual, whereas naloxone is most likely to be administered by or to a peer. Internationally, the preferred method of increasing availability to the public has been to implement peer-based training programmes through needle exchanges, prisons or addiction treatment centres. These programmes involve drug users and/or their peers and families receiving training in overdose identification and naloxone administration, upon completion of which they are given a naloxone kit to take home with them. The Government is yet to consider whether any such programmes should be designed, funded and implemented in New Zealand.

Despite these reservations, reclassification decisions should be made based on the MCC criteria. When considering the risks of a product compared with the benefits of access, we note that there is limited direct risk of harm as a result of making naloxone available as a restricted medicine. It is low risk with rare adverse reactions and no addictive or diversion potential.

We consider the following support needs to be provided when naloxone is dispensed:

- Naloxone is only one component of overdose treatment, alongside other measures such as first aid training and encouraging people to call ambulances without delay. Even if naloxone has been administered, an ambulance should always be called to provide life-saving ventilation and medical observation. It is important that supply of naloxone is accompanied by these messages.
- Currently approved naloxone products are injectable, carrying some risk of non-sterile injection and damage due to poor injection technique. Supply of naloxone injections by health professionals could ensure that advice on appropriate use can be provided, and an assessment of the consumer's capability to use the product appropriately (NB: It may be more desirable for other methods of administration to be available, however the availability of naloxone products is dependent on commercial sponsors marketing their product in New Zealand).

- The target users of naloxone will be intravenous drug users. As well as potential addiction issues, this population may also be experiencing other life and health difficulties. Successful interaction with this population would be sensitive to their needs and context.

If pharmacists can deliver this support, we conclude that reclassification may be appropriate as part of a suite of considerations to allow greater access to naloxone.

Action

The Ministry requests that the MCC take its position into account in its deliberations.

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AT THE HEART OF THE MATTER, NZ DRUG FOUNDATION.
Te Tūāpapa Tarukino o Aotearoa

5 April 2016

Andrea Kerridge
Secretary
Medicines Classification Committee
Ministry of Health

by email: committees@moh.govt.nz

Dear Andrea

Naloxone – new restricted/pharmacist only classification

This comment for the Medicines Classification Committee's (MCC) consideration at its 55th meeting, relates to agenda item '8.2.1 (d) Naloxone'. It is provided on behalf of the New Zealand Drug Foundation's Opioid Overdose Advisory Group.

The Drug Foundation is committed to increasing access to the opioid antagonist naloxone, to reduce deaths and harm from opioid overdose. To support this aim, the Foundation has formed a group with broad professional and personal interests in preventing opioid overdose, including representatives from treatment, harm reduction and drug consumer perspectives. The group's members and their professional affiliations are listed at the end of this letter.

The Opioid Overdose Advisory Group strongly encourages the MCC to follow the Australian decision and support a new restricted/pharmacist only classification entry for naloxone. The group considers this is a key step in increasing access to naloxone in New Zealand and addressing preventable opioid overdose deaths and harm. Naloxone's current prescription medicine classification should also be retained, as is the case in Australia.

Opioid overdose in New Zealand

New Zealand has around 37 recorded accidental opioid overdoses per year, excluding suicides[1]. This is about half of all drug related deaths[2]. However, this is likely to be a conservative figure due to:

- data limitations around coding 'accidental poisoning' deaths
- multiple factors leading to deaths - e.g. often poly drug use is a contributing factor or the physical cause of death such as 'respiratory depression' is recorded

[1] Ministry of Health, *Number of accidental poisoning and mental and behavioral disorder deaths where opioid poisoning was recorded on the death record, 2004-2011*, Offical Information Act request (2015).
[2] Ministry of Health, *Rate of adverse events to opiates in the treatment of chronic pain (2004-2010)*, Official Information Act request: H201500068 (2015).

- the sensitive nature of these deaths, which may lead to pressure not to explicitly record an opioid-related death.

True opioid overdose death rates may be around double what are officially recorded.[3]

With higher levels of opioids prescribed to manage pain internationally, there has been a corresponding rise in harm from both illicit and prescribed opioid use.[4] While New Zealand may not currently be experiencing a dramatic rise in or level of opioid overdose deaths, opioid prescriptions are increasing significantly here.[5] This brings inherent risks. New Zealand's rate of class B opioid prescribing rose from seven prescriptions per 100 people in the population in 2006 to 12 prescriptions per 100 people in 2013, and from 0.9 percent of the population to 1.6 percent of the population receiving a class B opioid prescription in the same timeframe.[6]

International best practice shows opioid overdose prevention strategies are essential to reduce overdose deaths and harm. Increasing access to naloxone, including by making it available via pharmacists, is one such important strategy. Overdoses are often witnessed by someone other than the person involved, enabling potential for emergency intervention.[7]

Naloxone and benefits of a restricted medicine classification

Naloxone is highly effective at reversing opioid overdose, beginning to reverse symptoms in a few minutes. It can be administered by intramuscular injection, nasal spray (currently unavailable in New Zealand) or intravenously and has no significant adverse side effects.[8]

If the person given naloxone is physically dependent on opioids they may go into withdrawal, but this can be managed through incremental dosing and observation.[9] Depending on the amount of opioids in a person's system, they may also relapse following initial naloxone administration and need further doses. It is therefore important that medical support is also sought immediately. However, giving an overdose victim naloxone quickly, prior to medical help being available, can be life-saving.

If naloxone is made available as a restricted medicine, the pharmacist can provide advice on correct administration and the need for post-administration medical support through a brief consultation and supporting information. A restricted medicine classification ensures purchasers must meet specific criteria and receive such a consultation. The mandatory consultation could be equivalent to a brief training in naloxone administration, which has proven effective.[10]

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[3] Phillip Coffin, "Under estimated and overlooked: A global review of drug overdose and overdose prevention," in *Global State of Harm Reduction 2010: key issues for broadening the response,* ed. Catherine Cook (International Harm Reduction, 2012).

[4] World Health Organisation, *Community management of opioid management,* (WHO, 2014), 1.

[5] Best Practice Advocacy Centre, "Oxycodone: how did we get here and how do we fix it?" *Best Practice Journal,* 62 (2014).

[6] Carina Walters, 'Opioid prescribing tends and associated mortality and morbidity in New Zealand 2006 to 2013', M.S. dissertation (Kings College London, 2014)

[7] Debra Kerr, et al., "Attitudes of Australian Heroin Users to Peer Distribution of Naloxone for Heroin Overdose: Perspectives on Interanasal Administration," *Journal of Urban Health,* 30 (2008): 352.

[8] Hospita, *DBL Naloxone Hydrochloride Injection USP,* (Medsafe, 2012).

[9] *Naloxone Hydrochloride Injection.*

[10] Emily Behar et al., "Brief overdose intervention is sufficient for naloxone distribution to opioid users," *Drug and Alcohol Dependence,* 148 (2015).

In New Zealand, naloxone is currently used mainly by advanced paramedics and in hospitals. It is available as naloxone hydrochloride for injection, a subsidised prescription-only medicine.[11] There are around 9000 injections of naloxone ordered by medical practitioners in New Zealand per year.[12]

However, naloxone is only funded by PHARMAC when ordered through a Practitioner Supply Order (PSO), five injections at a time. Under PSO guidelines, naloxone is available for "emergency use, teaching and demonstration purposes and for provision to certain patient groups where individual prescriptions are not practicable."[13]

Naloxone could technically be made widely available for 'patient groups' (such as people who inject illicit opioids) as a preventative health measure. But this is under doctor's discretion and does not appear to be common practice. Further, there are social and financial barriers, particularly for illicit drug users, to discuss their drug use with a medical practitioner and receive an individual prescription for naloxone.

Pharmacist provision is also useful for allowing concerned partners, friends, family members and fellow drug users to have naloxone on hand where necessary. This removes the barriers presented to all these groups in accessing naloxone through a prescription. Further, with pharmacists being key providers, accessibility is extended to people taking prescription opioids who would not necessarily be involved in addiction treatment services, through which they otherwise might be able to access naloxone.

International best practice

Naloxone has been used since the 1960s and is listed as an essential medicine by the World Health Organisation (WHO).[14] Over the last twenty years there has been consistent international action to increase naloxone availability beyond hospitals, aiming to reduce preventable deaths.

The United Nations Office on Drugs and Crime (UNODC) and WHO released a discussion paper on best practice for opioid overdose prevention in 2013. These organisations argued that fatal overdoses can be "easily averted through the use of naloxone, a safe and non-abusable substance."[15] The papers' major recommendation was to ensure people have access to naloxone if they are likely to be in a situation where they could administer it to save someone's life.[16]

Internationally, naloxone is a 'corner-stone' of opioid overdose prevention strategies and is frequently an aspect of harm reduction programs.[17] There is consensus on naloxone's

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[11] *Naloxone Hydrochloride Injection.*
[12] Ministry of Health, *PHARMAC subsidised, community dispensed, naloxone hydrochloride,* (2015).
[13] "Glossary." *PHARMAC.* Updated April 2015. http://www.pharmac.health.nz/tools-resources/glossary/.
[14] World Health Organisation, *WHO List of Essential Medicines,* (2013).
[15] United Nations Office on Drugs and Crime, *Opioid overdose: preventing and reducing opioid overdose mortality,* (UNODC/WHO, 2013), 7.
[16] *Community management of opioid management,* 9
[17] European Monitoring Centre for Drugs and Drug Addiction, *Preventing opiate overdose deaths with take-home naloxone.* (Publications office of the European Union, 2016).
http://www.emcdda.europa.eu/publications/insights/take-home-naloxone

usefulness, with a consistent correlation between increased access to the drug and decreasing overdose deaths.[18] [19]

Naloxone classification internationally

Internationally there has been wide experimentation around how to reduce overdoses by increasing access to naloxone. This has occurred primarily through providing:

- training and naloxone kits for emergency first responders
- opioid user peer-based training and take-home naloxone
- pharmacy-based access.

While the first two of these approaches can occur while naloxone is a prescription medication, that classification still hampers access and easier implementation of harm reduction approaches.

In most of Europe and areas of the United States (US) where naloxone is a prescription only drug, peer based training with take-home naloxone requires medical oversight and use of doctor's standing orders. This reduces the flexibility around how and when training can be provided. It also requires the person receiving the naloxone to go on record as receiving it, which may imply they use illegal opiates. Further, the prescription is often written for the opioid user them self, who will be unable to self-administer naloxone during an overdose.

These barriers to access have been reduced in Australia, Canada, some states of the US and Scotland, with availability from pharmacists. In Scotland, this has widened the range of access points for naloxone, with pharmacists able to distribute naloxone to key patient groups.[20] The Scottish pilot had high rates of people returning for additional naloxone following it being used (12% in pharmacies compared to 4% resupply from outreach teams) suggesting a high number of overdoses prevented.[21]

In Rhode Island, US, pharmacist provision has been a key strategy in addressing overdoses from prescription opiates. This has occurred by reaching people filling prescriptions and/or people who a peer-based training programme does not resonate with.[22] The increase of pharmacy-based provision is considered to be a key factor in reducing the increasing levels of overdose, with correlation between naloxone distributed (by all approaches) and the reduction in fatal overdoses.[23]

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[18] European Monitoring Centre for Drugs and Drug Addiction, *Preventing fatal overdoses: a systematic review of the effectiveness of take-home naloxone.* (Publications office of the European Union, 2015).
[19] *Opioid overdose: preventing and reducing opioid overdose mortality.*
[20] Hunter, Carol. "Injecting Equipment Provision (IEO) Pharmacy Naloxone Training Pilot." (2014). http://www.sdf.org.uk/resources/presentations/#2015
[21] Ibid.
[22] Green, Traci et al. "Orienting patients to greater opioid safety: models of community pharmacy-based naloxone." *Harm Reduction Journal* (2015).
[23] Ibid, 5.

Health Canada has also very recently revised the listing for naloxone on its Prescription Drug List to make it available from pharmacies, effective from 22 March 2016[24]. It had acknowledged that "The large increase in opioid overdose episodes has prompted the provinces to design programs to provide greater access to naloxone at the site of the overdose, either through first responders or "take-home programs". These programs are hindered by the prescription status of naloxone."[25]

We thank the MCC for its consideration and trust our comment is useful to the Committee for its deliberations.

Yours sincerely

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[24] Health Canada, 'Notice: Prescription Drug List (PDL): Naloxone', Health Canada [website] (22 March 2016) http://www.hc-sc.gc.ca/dhp-mps/prodpharma/pdl-ord/pdl-ldo-noa-ad-naloxone-eng.php, para. 1, accessed 1 April 2016.

[25] Health Canada, 'Notice: Prescription Drug List (PDL): Naloxone', Health Canada [website] (14 January 2016) <http://www.hc-sc.gc.ca/dhp-mps/consultation/drug-medic/pdl_ldo_consult_naloxone-eng.php>, para. 3, accessed 1 April 2016.