



Australian Government

Department of Health

Therapeutic Goods Administration

Codeine re-scheduling

Regulation Impact Statement

Version 1.1, December 2016

Office of Best Practice Regulation (OBPR) ID number: 19826

TGA Health Safety
Regulation

A decorative graphic consisting of several overlapping, wavy lines in shades of blue and green, flowing from the left side of the page towards the right, positioned below the TGA logo.

Copyright

© Commonwealth of Australia 2016

This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the *Copyright Act 1968* or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the TGA Copyright Officer, Therapeutic Goods Administration, PO Box 100, Woden ACT 2606 or emailed to <tga.copyright@tga.gov.au>.

Abbreviations

ACMS	Advisory Committee for Medicines Scheduling
ACSOM	Advisory Committee on the Safety of Medicines
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
AHMAC	Australian Health Ministers' Advisory Council
AMA	Australian Medical Association
API	Active Pharmaceutical Ingredient(s)
ARTG	Australian Register of Therapeutic Goods
ASMI	Australian Self Medication Industry
AusPAR	Australian Public Assessment Report
BAU	business as usual
CACC	combination analgesic containing codeine
CATAG	Council of Australian Therapeutic Advisory Groups
CCA	codeine-containing analgesics
CMI	Consumer Medicines Information
DHC	dihydrocodeine
EMA	European Medicines Agency
FDA	Food and Drug Administration (USA)
GMP	Good Manufacturing Practice
GI	gastrointestinal
GP	general practitioner
MBS	Medicare Benefits Schedule
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
NDPSC	National Drugs and Poisons Schedule Committee
OBPR	Office of Best Practice Regulation
OTC	over the counter
PBS	Pharmaceutical Benefits Scheme
PGA	The Pharmacy Guild of Australia
PI	Product Information
PIL	Patient Information Leaflet
PSA	Pharmaceutical Society of Australia
QALY	quality adjusted life year

RACGP	Royal Australian College of General Practitioners
RACP	Royal Australian College of Physicians
RASML	Required Advisory Statements for Medicine Labels
RBE	Regulatory Burden Estimate
RBM	Regulatory Burden Measure
RIS	Regulation Impact Statement
RTM	real-time monitoring
SHPA	Society of Hospital Pharmacists of Australia
SmPC	Summary of product characteristics
SPF	Scheduling Policy Framework
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons; Poisons Standard
TGA	Therapeutic Goods Administration
WHO	World Health Organization

Contents

Executive summary	10
Introduction	12
What is the problem?	13
What is codeine?	14
Codeine is a prodrug	14
How is codeine used?	15
Analgesia	16
Cough and cold preparations	16
What are the health concerns with codeine use?	16
Health Safety Reports	16
Morbidity and death	20
Dependence and addiction	22
International regulation of codeine	23
United States of America (USA)	23
Europe and Asia	23
United Kingdom	24
Canada	25
Summary of international regulation of codeine and implications for Australia	26
Australian risk management framework	27
Standard for the Uniform Scheduling of Medicines and Poisons	27
Scheduling of medicines	28
Scheduling factors	28
Current scheduling status of codeine	30
Historical scheduling of codeine	31
How effective were the scheduling changes for codeine in 2010?	32
Is the current scheduling of codeine best practice?	33
Regulatory options	35
What are the regulatory options and scenarios being considered?	36
Why are regulatory options being considered?	37
Real-time monitoring programs	38
MedsASSIST program	39
Regulatory and health economic impact models	41

Regulatory impact model	42
Inputs and assumptions	42
Baseline assumptions	44
Health economic impact model	46
How the health economic model works	46
Sources of complexity – interdependency and data paucity	47
Sources of uncertainty	48
Five main considerations for economic model	50
Sensitivity analyses	60
Results	60
Individual options	61
Option 1: Status quo	61
Impacts	62
Regulatory costs	62
Health costs and benefits	62
Option 2: Reduce pack size of Schedule 2 and new label warning	63
Regulatory cost assumptions for Option 2	64
Impacts	65
Regulatory costs	66
Health costs	66
Health benefits	66
Option 3: Up-schedule Schedule 2 to 3, reduce pack size and new label warning	67
Regulatory cost assumptions for Option 3	68
Impacts	69
Regulatory costs	69
Health costs	70
Health benefits	70
Option 4: Up-schedule Schedule 2 to Schedule 4	70
Regulatory cost assumptions	71
Impacts	73
Regulatory costs	74
Health costs	74
Health benefits	74
Option 5: Reduce pack size of Schedule 3 and new label warning	75
Regulatory cost assumptions	76
Impacts	76

Regulatory costs	77
Health costs	77
Health benefits	77
Option 6: Up-schedule Schedule 3 to Schedule 4	78
Regulatory cost assumptions	78
Impacts	80
Regulatory costs	81
Health costs	81
Health benefits	81
Regulatory burden estimate (RBE) for each option	84
Regulatory burden estimate (RBE) for each scenario	84
Net benefit for each scenario	85
Scenario 1 (Option 1: status quo)	86
Scenario 2 (Options 2 and 5: reduce pack size of Schedule 2 and Schedule 3 and new label warning)	87
Scenario 3 (Options 3 and 5: up-schedule Schedule 2 to Schedule 3 and reduce pack size for Schedule 3)	88
Scenario 4: (Options 4 and 6: OTC codeine not available)	88
Predicted costs to deliver health benefits	90
Overview of consultation activities	91
Expert advice from Advisory Committee on Medicines Scheduling	91
Formal consultation periods regarding the re-scheduling of codeine	92
Pre-meeting (July 2015 ACMS meeting) public consultation	94
Interim decision public consultation	94
Additional consultation period	95
Summary of public submissions	95
Public submissions supporting up-scheduling	95
Public submissions opposing up-scheduling	96
General practitioner considerations	97
Targeted consultations with industry and peak bodies	98
Interviews with industry	98
Interviews with peak bodies	99
Topic 1 - Product strategy	99
Topic 2 - Market response	99
Topic 3 - Reduced pack size	100

Topic 4 – New warning labels-----	100
Topic 5 – Updated listings -----	101
Topic 6 – Implementation timeframes-----	101
Implementation timeframe _____	102
Labelling changes _____	103
Stock turnover _____	103
Product strategy and diversification _____	103
Reduce pack size _____	103
OTC C1/C2 level applications _____	103
Applications to register a prescription medicine (Schedule 4) _____	103
What is the preferred scenario? _____	105
Appendix A _____	108
Interview questionnaire for sponsors _____	108
Context-----	108
Scenarios -----	108
Topic 1 – Product strategy-----	109
Topic 2 – Market response -----	110
Topic 3 – Reduced pack sizes -----	110
Topic 4 – New warning labels-----	110

Table of figures

Figure 1: Mean availability of opioids for pain management in 2001-2013.....	27
Figure 2: Patient/consumer groups used in the health economic modelling.....	51
Figure 3: Potential patient actions and therapy options in response to pain.....	55
Figure 4: Determining key modelling parameters.....	59
Figure 5: Option 6 outcomes for acute and chronic users of current Schedule 3 codeine	83
Figure 6: Public consultation process for codeine and the timeline of major decision points	93
Figure 7: Implementation timeframe	102

Table of tables

Table 1: Summary of regulatory options.....	36
Table 2: Summary of scenarios	36
Table 3: Results of PGA's MedsASSIST program	39
Table 4: Number of products containing codeine phosphate [actual and (adjusted)] listed in the ARTG by Schedule	45
Table 5: Consumer share of market and share of sales by two hypothetical consumer groups....	50
Table 6: Type of current consumers and their pattern of use for Schedule 3 medicines only	54
Table 7: Requirements for codeine in the current Poisons Standard	62
Table 8: Regulatory impacts of Option 2	63
Table 9: Average annual regulatory costs (from business as usual) for Option 2	66
Table 10: Regulatory impacts of Option 3	67
Table 11: Average annual regulatory costs (from business as usual) for Option 3.....	70
Table 12: Regulatory impacts of Option 4	71
Table 13: Average annual regulatory costs (from business as usual) for Option 4.....	74
Table 14: Regulatory impacts of Option 5	75
Table 15: Average annual regulatory costs (from business as usual) for Option 5.....	77
Table 16: Regulatory impacts of Option 6	78
Table 17: Average annual regulatory costs (from business as usual) for Option 6.....	81
Table 18: Average annual regulatory costs (from business as usual) by sector for all options.....	84
Table 19: Average annual regulatory costs (from business as usual) by sector for all scenarios.	85
Table 20: Regulatory (for first year, 2017 and the period 2017-2026) as well as the economic costs and benefits (for the period 2017-2026) for each option and scenario (\$million)	86
Table 21: Summary of implementation timeframes.....	104

Executive summary

Codeine is a commonly used medicine of abuse. Codeine in over the counter (OTC) combination analgesics and codeine dependence contributes to severe adverse health outcomes associated with overdose of other active constituents such as paracetamol or ibuprofen. There is substantial evidence of harm from abuse or misuse of codeine-containing medicines, including liver damage, gastrointestinal perforations, respiratory depression and death. The Department of Health, through the Therapeutic Goods Administration (TGA), has reviewed OTC access to codeine-containing medicines in Australia to ensure that regulation protects public health and safety.

Currently the options being considered to address this issue are grouped into 4 scenarios:

Scenario 1: No change to the status quo.

Scenario 2: Schedule 2 and Schedule 3 entries for codeine to be amended to reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction.

Scenario 3: The current Schedule 2 entries for codeine in cough and cold preparations to be up-scheduled to Schedule 3. All Schedule 3 entries to be amended to reduce the pack size to not more than 3 days' supply, and include a label warning that codeine can cause addiction.

Scenario 4: Schedule 2 and Schedule 3 entries for codeine to be up-scheduled to Schedule 4.

In addition to extensive public consultation by the TGA prior to and during preparation of this RIS, the consultancy firm KPMG produced a regulatory costing model and an economic and social impacts model (health economic model). Each of these models were informed by a range of sources, including industry and peak body consultations, as well as guidance from the TGA and the OBPR. A summary of the results from the modelling is presented in the following table.

Regulatory (for first year, 2017 and the period 2017-2026) as well as the economic costs and benefits (for the period 2017-2026) for each option and scenario (\$million)

		Scenario 2		Scenario 3		Scenario 4	
		Option 2	Option 5	Option 3	Option 5	Option 4	Option 6
Regulatory costs (average annual)	Option	(\$0.05)	(\$0.13)	(\$10.14)	(\$0.13)	(\$10.24)	(\$2.21)
	Scenario	(\$0.18)		(\$10.27)		(\$12.45)	

For the 10-year period from 2017-2026 the following costs and benefits have been estimated:

Regulatory costs (not discounted)	Option	(\$0.50)	(\$1.30)	(\$101.40)	(\$1.30)	(\$102.40)	(\$22.10)
	Scenario	(\$1.80)		(\$102.70)		(\$124.50)	
Health economic costs (7% discounted)	Option	(\$20.70)	(\$409.87)	(\$14.49)	(\$409.87)	(\$56.03)	(\$209.87)
	Scenario	(\$430.57)		(\$424.36)		(\$265.90)	
Health economic benefits (7% discounted)	Option	0	0	0	0	\$243.95	\$5,353.17
	Scenario	0		0		\$5,597.12	
Net benefit (7% discounted)	Option	(\$21.20)	(\$411.17)	(\$115.89)	(\$411.17)	\$85.52	\$5,121.20
	Scenario	(\$432.37)		(\$527.06)		\$5,206.72	

Source: KPMG 2016, Table ES2 (Annex 1)

Only Scenario 4 (Options 4 and 6) results in a net benefit to society. The economic benefits are driven by gains in quality of life, deaths prevented, and net financial savings to consumers; for example, those consumers who substitute OTC codeine medicines with paracetamol and/or ibuprofen, post regulatory change. This positive net benefit for Scenario 4 is robust to a wide range of sensitivity analyses, including the following set of cost maximising and benefit minimising assumptions:

- if no deaths are prevented
- if the costs of gaining any quality of life improvements, for example through improved treatment for chronic pain, are increased by 80%
- if the quality of life gain from treatment is reduced by 80%.

The variables that the net benefit was most sensitive to were the average Quality Adjusted Life Year (QALY) gain resulting from additional treatment received for pain symptoms, and the number of repeat scripts. The economic model was only moderately sensitive to the discount rate, number of deaths prevented, and the co-payment for GP and specialist consultations.

Scenario 4 will provide the greatest protection of public health and safety as a result of positive changes in consumer purchasing behaviour, raising awareness of codeine dependency through education, and the increased exploration of alternative therapeutic and treatment pathways for pain management. This scenario also delivers a net economic benefit to society significantly greater than any other scenario.

The implementation of Scenario 4 involves up-scheduling codeine entries from Schedules 2 and 3 to Schedule 4, the implication of which is that no codeine-containing products would be available without a prescription. The minimum implementation timeframe for Scenario 4 is 12 months. At this time, the estimated regulatory burden is expected to be less than \$12.5 million per annum, which will be offset in the ensuing couple of years.

Introduction

Due to significant health risks associated with over the counter (OTC) codeine-containing medicines, the medicine's scheduling delegate of the Department of Health is considering re-scheduling codeine in the Poisons Standard to change the way codeine-containing medicines are made available to the consumer.

In October 2015, the delegate made an interim decision that all medicines containing codeine currently available OTC (Schedules 2 and 3) would be up-scheduled to prescription only medicines (Schedule 4). In November 2015, the delegate announced that a decision on the re-scheduling of codeine would be delayed to allow a more thorough consideration of the numerous submissions and the broader implications to current products in the market. In addition to the re-scheduling of codeine, further public submissions were requested on other options, such as reducing in pack size and including a warning statement on the packaging.

To better inform the regulatory, social and health impacts of any change to the scheduling of codeine, a Regulation Impact Statement (RIS) has been completed. An external consultant team has modelled the regulatory costing and economic and social impacts of the codeine re-scheduling options. During several public consultations by the Therapeutic Goods Administration (TGA) regarding the proposed codeine re-scheduling, feedback was received from individual consumers, healthcare professionals and the pharmaceutical industry, as well as state and territory jurisdictions. During the preparation of the RIS, further consultations were held with key stakeholders to document the potential business process impacts, to inform the development of the modelling, and to determine any implementation timeframes that might be required by industry to comply with any change in codeine scheduling. These consultations aimed to minimise the regulatory impact and to address identified issues, including the risk to consumer safety if no action is taken.

The international restrictions of codeine medicines applied by overseas jurisdictions, including the USA, Canada and Europe were reviewed. Due to harm from abuse and misuse of codeine, including dependency and death, medicines containing codeine are specifically regulated in many countries. Regulatory controls include limits on pack sizes, label warnings on packaging, warnings in consumer information leaflets, and limiting the availability of codeine-containing medicines to prescription only.

Stakeholders participating in these consultations were industry peak bodies and key healthcare professional and consumer groups including:

- Generic Medicines Industry Association (now the Generic and Biosimilar Medicines Association)
- Medicines Australia
- Australian Self Medication Industry (ASMI)
- The Pharmacy Guild of Australia (PGA)
- Pharmaceutical Society of Australia (PSA)
- Society of Hospital Pharmacists of Australia (SHPA)
- Council of Australian Therapeutic Advisory Groups (CATAG)
- Australian Medical Association (AMA)

The RIS summarises the consultation process that has been undertaken with stakeholders including consumers, healthcare professionals and industry to explore the available options to minimize regulatory impacts of up-scheduling codeine.

The regulatory burden and potential social and financial impacts on public, industry, and government have been considered. The RIS concludes with a recommended scenario that affords the best protection of public health and safety, balanced against any regulatory burden placed on stakeholders. Not all aspects of the modelling, such as social and economic burdens are able to be considered by the Secretary of the Department of Health or their delegate in making their decision. Scheduling decisions are made according to subsection 52D(2) of the [Therapeutic Goods Act 1989](#) (TG Act) which takes into account relevant matters of public health as set out under section 52E of the Act. These matters include the risks and benefits of the use of a substance, the purposes for which a substance is to be used, the substance's toxicity, dosage, formulation, labelling, packaging, presentation, and any potential for abuse. Guidance of the matters to be considered by the delegate are outlined in the [Scheduling Policy Framework \(SPF\)](#).

What is the problem?

What is the problem?

Codeine is a commonly used medicine of abuse. Low-dose codeine (less than 30 mg) is currently available in a number of formulations in pharmacies over the counter (OTC) for consumers to self-administer. These include cough and cold preparations, and analgesic preparations combined with other pain relief medicines such as paracetamol or ibuprofen. There is substantial evidence of harm from the abuse and misuse of low-dose codeine-containing medicines.

The presence of low-dose codeine in widely accessible OTC combination medicines, and the development of tolerance and subsequent dependence on codeine, contributes to severe health outcomes, including liver damage and death. Low-dose codeine-containing medicines are not intended to treat long term conditions; however, public consultation has indicated that this is how most consumers use these medicines.

Additionally, some individuals, especially children, experience serious adverse reactions when given codeine, such as difficulty breathing and death.

For a majority of individuals, there is little evidence that low-dose codeine medicines are more effective than alternative medicines without codeine.

Given these issues, it is clear that alternative regulatory controls are required to drive public health benefits that outweigh the known risks of codeine use.

Following announcements on the TGA website of proposed changes in codeine scheduling, and safety information describing the health concerns relating to OTC codeine use, misuse and abuse, over 230 public submissions have been received (see '[Overview of consultation activities](#)' p. 91 for further details). The opinions expressed in the public submissions were polarised, and when similar opinions that support regulatory action were grouped they generally expressed the following thoughts and feelings:

'The current listing of codeine-containing combinations with nonopioids as Schedule 3 medications fails to protect the Australian community from the harmful side effects of these combination preparations with marginal analgesic benefit.' – Pain medicine specialist

'Our son went on to develop a serious addiction which resulted in him drinking the entire contents of a 200ml bottle of xxx cough syrup in one sitting, several times a week... When he couldn't obtain xxx, he would buy 48 tablet packs of Panadeine Forte or similar paracetamol/codeine preparations... Please count us as a family devastated by the over-the-counter supply of codeine products to teenagers.' - Consumer

Conversely, public submissions from those consumers that oppose any regulatory change such as up-scheduling (approximately 77%) express views that are similar to that below:

'It is simply wrong that I should have to pay a non-refundable gap of around \$40 simply to get a prescription for a medication that I, like the vast majority of people in this country, use sparingly and responsibly.'

This indicates that an emphasis on consumer education will be critical following any changes in codeine scheduling to better inform the public about the potential harms of chronic codeine use, especially when used in combination products.

What is codeine?

Codeine is an opioid drug closely related to morphine and, like morphine, is also derived from opium poppies. Codeine is contained in the World Health Organization (WHO) Model list of essential medicines as an important medicine to be provided in a basic healthcare system. There are many forms of codeine, including various salts (phosphate, phosphate hemihydrate, hydrochloride, sulfate, camsilate and hydrobromide forms) and there are also derivatives such as acetyldihydrocodeine, codeine-*N*-oxide, dihydrocodeine, and norcodeine. These derivatives are outside the scope of the current RIS; however, they may need to have their scheduling reconsidered once a scheduling decision is made for codeine. Of the salts, codeine phosphate hemihydrate is the dominant form in the Australian marketplace today.

Codeine is an old and commonly used analgesic for mild and moderate pain and is used in many medicines across both the prescription and over-the-counter (OTC) markets. In the prescription medicine context, high dose codeine products (30* mg to 120 mg/dose), either alone or in combination with paracetamol, provide a good level of strong pain relief for some people with cancer pain, post-operative pain and other acute pain conditions.^{1,2}

In comparison, low-dose codeine products (10-12* mg/unit dose, referred to as *low-dose codeine medicine* hereafter) in OTC products, are used to manage milder pain conditions such as migraine, headache, dental pain,³ or for the management of cold and flu symptoms (including cough).

Codeine is a prodrug

Codeine itself is a weak analgesic in its original form, and must be metabolised to its active metabolite, morphine, by the liver enzyme cytochrome P450 2D6 (CYP2D6) to have a therapeutic effect. Codeine should therefore be regarded as a prodrug that requires

* The concentration of codeine on the medicine pack may be different due to the salt component.

¹ Philip J Wiffen, Roger Knaggs, Sheena Derry, Peter Cole, Tudor Phillips, R Andrew Moore, R Andrew Moore, *Cochrane Database of Systematic Reviews*, 2016

² Toms L, Derry S, Moore RA, McQuay HJ. *Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults*. *Cochrane Database of Systematic Reviews*, 2009

³ Ahlstrom U, Fahraeus J, Quiding H, Strom C. Multiple Doses of Paracetamol Plus Codeine Taken Immediately After Oral Surgery. *Eur J Clin Pharmacol* 1985; 693-696.

bioactivation before an effect is observed. Codeine's effectiveness depends on the individual's ability to metabolise codeine to morphine.

There are a number of genetic variants of CYP2D6, resulting in large variability in individual responses to codeine. At one extreme are poor metabolisers, who lack functional CYP2D6 (5-10% of the population) and experience very little therapeutic effect from codeine. At the other extreme, *ultrarapid* metabolisers (up to 10% of the Caucasian population and 30% of the African population)⁴ have increased conversion of codeine to morphine, leading to a higher risk of toxicity.

Since codeine was first made available and scheduled, the ability to measure CYP2D6 polymorphism (i.e. the existence of variable forms of the gene within the population) has become possible, but it is not a routinely conducted clinical test due to its complexity and expense.

While morphine is a strong opioid analgesic, the analgesic efficacy of codeine itself is very low, as demonstrated by the lack of analgesic effect in poor metabolisers. Since very few individuals who purchase OTC codeine medicines are aware of their own CYP2D6 status, the dosing instructions are inappropriate for many consumers, with specified doses being too low to achieve an analgesic effect for some and too high for others.

Published reviews on the efficacy of codeine when given in small to moderate doses (30 mg or less), either alone or in combination with another analgesic such as paracetamol or a non-steroidal anti-inflammatory (NSAID), have had varied results. For example, a review of nine randomised controlled trials of analgesia post-laparotomy showed no greater efficacy of paracetamol plus 30 mg codeine compared with a variety of NSAIDs given alone.⁵

How is codeine used?

Codeine may be used as an analgesic for the relief of mild to moderate pain, and for the symptomatic relief of non-productive cough. As a prescription medicine containing greater than 30 mg of codeine, these medicines provide a good level of pain relief in some people experiencing strong pain, such as cancer pain.

Combination medicines containing codeine are widely available OTC in pharmacies and are self-selected by consumers to manage mild pain conditions, such as headaches or backache. Consumers appear to choose low-dose codeine combination analgesics for strong pain relief, as they are marketed to be effective for strong pain, while simple pain relievers such as paracetamol and ibuprofen are thought to provide more general pain relief. However, there is limited data on the incremental effectiveness of combination medicines that contain low-dose codeine when compared to other analgesics.

With respect to cough and cold medicines containing codeine, often consumers choose such products to relieve a cough (cough suppressant). However, there is limited information from good quality clinical trials to indicate that codeine-containing cough suppressants are effective for treating coughs in children.⁶ Indeed the health risks associated with codeine cough suppressants used in children are significant and therefore should not be used in children younger than 6 years.

⁴ Iedema J (2011) Cautions with codeine, Australian prescriber 34: 133-135.

⁵ Nauta M, Landsmeer M, Koren G et al. Codeine-acetaminophen versus non-steroidal anti-inflammatory drugs in the treatment of post-abdominal surgery pain: a systematic review of randomized trials. Am J Surg 2009; 198:256-261.

⁶ <http://www.nps.org.au/medicines/respiratory-system/cough-and-cold-medicines/for-individuals/types-of-cough-medicines>

Analgesia

In oral pain relief OTC preparations, codeine phosphate (usually 8 mg per dosing unit) is often combined with a non-opioid analgesic such as aspirin, ibuprofen or paracetamol. The approved indication for Schedule 3 codeine products is for the '*temporary relief of strong pain and discomfort associated with a number of different medical conditions*'. However there is significant use of Schedule 3 codeine products for long term relief of chronic pain and a number of public submissions by consumers have noted that this is how they use it.

Opioid analgesics are generally not considered suitable for a first-line therapy to treat chronic non-cancer pain, nor are they appropriate for long-term use.⁷ Instead, clinical therapeutic guidelines for analgesia⁸ and proponents of up-scheduling state that the management of chronic non-cancer pain would be better achieved via medical practitioner evaluation and advice with regards to appropriate pharmacological and non-pharmacological treatments.

Cough and cold preparations

Codeine or its salts (especially the phosphate salt)⁹ are given orally in the form of linctuses (low-dose, 5 mg/mL) for the relief of cough. Cough and cold preparations containing codeine are often compounded with phenylephrine, and may include additional non-opioid analgesics or other therapeutic substances.

What are the health concerns with codeine use?

Information from within Australia and from other comparable international regulators indicates that codeine-containing medicines are being abused and/or inappropriately used. Over the last decade this has resulted in a rise in morbidity and deaths¹⁰ associated with liver damage, gastrointestinal perforations and respiratory depression.

Health Safety Reports

The TGA has undertaken or commissioned three separate reviews which have included the efficacy and/or safety of codeine over the past 7 years. The outcomes and recommendations of these reviews are provided in the following paragraphs.

⁷ Opioid prescription in chronic pain conditions: Guidelines for South Australian general practitioners (GPs). These guidelines were produced by Drug & Alcohol Services South Australia, the Flinders Medical Centre Pain Management Unit, and the Royal Adelaide Hospital Pain Management Unit with funding under the Ministerial Council on Drug Strategy Cost Shared Funding Model. 2008. www.dassa.sa.gov.au/goto/ddu, accessed on 21 September 2016.

⁸ Therapeutic Guidelines Ltd (eTG July 2016 edition): Analgesic, <https://tgldcdp.tg.org.au/viewTopic?topicfile=pain-clinical-assessment>, accessed on 21 September 2016.

⁹ The Poisons Standard states that in the case of codeine, the concentration, strength or quantity is calculated as anhydrous codeine. The concentrations referred to in the Schedules therefore refer to anhydrous codeine. However, codeine is often present in products as codeine phosphate, and the strength listed on packaging usually refers to codeine phosphate, not codeine. Schedule 4 refers to 30 mg or less of codeine. This is equivalent to approximately 39 mg codeine phosphate. Schedule 3 refers to 12 mg or less of codeine. This is equivalent to 15.9 mg codeine phosphate. Schedule 2 refers to 10 mg or less of codeine. This is equivalent to 13 mg codeine phosphate.

¹⁰ Roxburgh A, Hall WD, Burns L, Pilgrim J, Saar E, Nielsen S and L Degenhardt. Trends and characteristics of accidental and intentional codeine overdose deaths in Australia. *Med J Aust* (2015) 203(7).

Safety and efficacy of registered over-the-counter (OTC) cough and cold medicines for children aged 2-12 years (TGA, 2012)

Between the years of 2009-2012, the TGA carried out a comprehensive review of the medical literature relating to the safety and efficacy of OTC medicines containing various substances for the symptomatic treatment of cough and cold in children aged less than 12 years. Codeine was considered as part of this review due to its purported antitussive activity. This review was published on the TGA website in 2012 (<https://www.tga.gov.au/otc-cough-and-cold-medicines-children-final-outcomes-tga-review>).

As a result of this review, the TGA concluded that there was a lack of evidence to support the efficacy of OTC cough and cold medicines in children under 12 years of age, although there was no immediate safety risk associated with their use in adults. Further, the potential risks of adverse reactions in children less than 12 years of age were high relative to the limited benefits. This conclusion was supported by the historical profile of adverse reactions in children under the age of 12, which included deaths associated with respiratory depression.

The review showed that the risks associated with OTC cough and cold medicines are greater in children aged less than 6 years compared to children between 6 and 11 years. These medicines therefore should not be used for treating children less than 6 years of age, and should only be administered to children aged 6-11 years on the advice of a doctor or pharmacist. Furthermore, all of these medicines should be in child-resistant packaging and labelled accordingly. The scheduling status of these medicines in the Poisons Standard should also be examined in order to determine if any changes are needed to their availability.

The recommendations resulting from this safety review included the introduction of new Required Advisory Statements for Medicine Labels (RASML), which came into effect in December 2015. Oral preparations containing codeine or any other active component indicated for cough, cold or flu that do not include dosage instructions for children aged under 12 years will read '*Do not give to children under 12 years of age.*' For example, oral preparations containing codeine indicated for cough, cold or flu will include dosage instructions for children aged from 'x' to 11 years (where 'x' is 6, 7, 8, 9, 10 or 11).

- When x = 11 '*Do not give to children under 11 years of age, except on the advice of a doctor, pharmacist or nurse practitioner*'
- When x < 11 '*Do not give to children aged between 'x' and 11 years of age, except on the advice of a doctor, pharmacist or nurse practitioner.*'

These requirements clearly indicate concern regarding the safety of codeine in OTC cough and cold preparations (Schedule 2) when given to children.

Subsequent to this initial review, two expert safety reports were commissioned by the TGA: *Safety review on codeine use in children and ultra-rapid metabolisers* (TGA, 2015) and *Investigating the efficacy and safety of over-the-counter codeine-containing combination analgesics for pain and codeine based antitussives*.¹¹ The following provides the outcomes and recommendations concluded by these expert reviews.

¹¹ CA Shaheed, CG Maher and A McLachlan. 'Investigating the efficacy and safety of over-the-counter codeine-containing combination analgesics for pain and codeine based antitussives.' <https://www.tga.gov.au/alert/review-efficacy-and-safety-over-counter-codeine-combination-medicines>. 21 March 2016. (this report is also referred to as the 'George Institute Report')

Safety review on codeine use in children and ultra-rapid metabolisers (TGA, October 2015)

The TGA's second safety review of codeine use in children (and also included ultra-rapid metabolisers) was published on the TGA website in October 2015. [TGA Pharmacovigilance and Special Access Branch Safety Review: Codeine use in children and ultra-rapid metabolisers. October 2015 [<https://www.tga.gov.au/alert/safety-review-codeine-use-children-and-ultra-rapid-metabolisers>].

This safety review considered the use of codeine-containing products in children and breastfeeding mothers, in the context of genetically determined ultra-rapid metabolism of codeine to morphine. Children who metabolise codeine to morphine ultra-rapidly are at a higher risk of accidental morphine overdose, which can lead to respiratory compromise and death. Children are more susceptible to respiratory problems than adults due to their immature airway anatomy. Children who have had an adenotonsillectomy for obstructive sleep apnoea may be particularly susceptible to opioid-induced respiratory depression in the post-operative period. Codeine that has been metabolised to morphine can also be ingested by infants through breast milk, causing risk of respiratory depression to infants of ultra-rapid metaboliser mothers who take codeine.

Internationally, deaths have been reported in children with ultra-rapid metabolism who were given codeine for analgesia post adenotonsillectomy, and for other indications. Deaths have also been reported internationally in breast-fed infants of mothers who are ultra-rapid metabolisers of codeine. However at the time of this review, there were no reported cases of respiratory compromise leading to deaths with paediatric codeine use in ultra-rapid metabolisers in the Australian post-market or coronial data.

The final recommendations of the safety review were:

- The use of codeine in children younger than 12 years of age for any indication, and in children 12-18 years post adenotonsillectomy for obstructive sleep apnoea should be contraindicated.
- Existing warnings contraindicating codeine use by breastfeeding mothers should be made consistent across all codeine-containing products.
- Warnings should be added to advise against using codeine if the individual is known to be an ultra-rapid metaboliser.
- Healthcare professionals, patients and caregivers should be educated regarding the variability of codeine efficacy, the possibility of ultra-rapid metabolism-related morphine overdose, and the signs of such, including respiratory depression.

These recommendations were supported by the TGA's Advisory Committee on the Safety of Medicines (ACSOM) at their meeting on 10 July 2015. ACSOM noted that the OTC availability of codeine-containing medicines supported a general perception in the community that codeine is safe and that there would need to be additional measures, such as education and possible up-scheduling, to achieve the desired outcome of risk reduction.

The independent expert safety committee emphasised the risks of respiratory depression and possible death in the context of ultra-rapid metabolism associated with codeine, with these risks outweighing the benefits of codeine use for all indications in children under the age of 12 years. Furthermore 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), and thus the risks relate to all children under the age of 12.

Other points made in the independent expert safety advice included:

- The risks associated with codeine outweigh the benefits 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 outlined above. This is consistent with both the FDA (USA) and EMA (Europe) positions, which contraindicate the use of codeine after adenotonsillectomy.
- 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.

In light of these safety review recommendations, the TGA has commenced implementation of label warning statements for all Schedule 4 codeine-containing medicines. Implementation of the recommendations for the remaining Schedule 2 and Schedule 3 products is on hold pending the current re-scheduling decision. If the scheduling decision is to maintain codeine-containing products as OTCs, a consultation on the above recommended warning statements may take place concurrently with any new statements that would come out of the scheduling decision.

Investigating the efficacy and safety of OTC codeine-containing combination analgesics for pain and codeine based antitussives (March 2016; George Institute review)

The aim of this systematic review¹² was to determine the efficacy and safety of OTC codeine combination analgesics for the treatment of any pain condition, or as an antitussive. A total of 14 randomised placebo-controlled trials of combination codeine analgesics or codeine based medicines [involving 788 participants] were included in this review. Ten of the trials evaluated the effects of codeine on various pain conditions and four trials evaluated codeine's antitussive effects. There is high quality evidence that combination codeine medicines provide clinically important pain relief in the immediate term (3 hours post ingestion), but it is unclear the level of incremental pain relief that was provided by the codeine component of these combination medicines.

In addition to the studies above, three trials compared combination codeine medicines with appropriate single ingredient comparators, two of which reported no statistically significant difference in analgesia, with one trial reporting a marked increase in analgesia attributable to codeine activity (refer to '*Morbidity and death*' below for more details). Some of the trials however, did not use the same-drug comparisons, comparing codeine-containing combination medicines with single ingredient analgesia medicines such as an NSAID plus codeine or paracetamol. In these trials, no information was presented for codeine-only medicines compared to combination medicines (such as NSAIDs or paracetamol) which made it difficult to evaluate the incremental effectiveness of codeine or to attribute any findings involving the efficacy of codeine alone.

Furthermore, this review found that codeine-based medicines reduce cough severity, but not frequency; however the evidence for this is very low quality.

¹² CA Shaheed, CG Maher and A McLachlan. 'Investigating the efficacy and safety of over-the-counter codeine-containing combination analgesics for pain and codeine based antitussives.'
<https://www.tga.gov.au/alert/review-efficacy-and-safety-over-counter-codeine-combination-medicines>.
 21 March 2016. (this report is also referred to as the '*George Institute Report*')

Morbidity and death

Morbidity

It is clear from publications, case studies, and anecdotal reports over the last couple of decades that morbidity from misuse of codeine-containing OTC products is a significant health problem, both internationally and in Australia. The misuse and abuse of codeine leads to the ingestion of excessive doses of the companion drugs (usually paracetamol or NSAIDs).

According to a recent survey from the National Drug Institute, the number of teenagers abusing medicines doubled between 2010 and 2013, with 41% of these teenagers reporting OTC codeine-combination medicine misuse.¹³

There are case reports of serious adverse effects and deaths from combination codeine medicines, particularly related to paracetamol-induced hepatotoxicity¹⁴ and NSAID-induced gastrointestinal (GI) ulceration.^{15, 16} The TGA Database of Adverse Event Notifications¹⁷ (sourced in early 2014) contained 59 cases of gastrointestinal ulcer or bleeding related to codeine/NSAID combinations, and 57 cases of hepatotoxicity from combination codeine/paracetamol products.

Opioid withdrawal symptoms upon cessation appear to propagate the cycle of misuse and dependency as evidenced in some case studies where opioid withdrawal was of notable concern.^{18, 19}

In a submission to the Department of Health in 2008, the Victorian Department of Health had identified 77 cases of codeine-ibuprofen analgesic misuse (50 tablets per day on average) over months to years (average 2.5 years) resulting in dependence and serious incidences of harm, including one death.²⁰ The Department of Health then requested that all state and territory health departments provide information on the abuse or misuse of codeine and ibuprofen combinations. Significant morbidity associated with the misuse of codeine-containing combination products was subsequently reported by every Australian state and territory. However, the data were not comprehensive and could not be formally analysed.

Frei *et al.*¹⁸ (2010) examined data on a series of 27 patients being treated for complications of prolonged use of supra-therapeutic (more than 6 months with a daily dose ranging between 34 and 47 tablets) OTC codeine-ibuprofen analgesics in Victoria between May 2005 and December 2008. Ten patients had GI complications attributed to ibuprofen, including one patient who required a gastrectomy; 4 patients had life threatening hypokalaemia and one patient had renal failure, requiring dialysis.

13 <https://ajp.com.au/news/teens-misusing-paracetamol-ibuprofen/> accessed November 2016

14 Lund C. et al. A one-year observational study of all hospitalized and fatal acute poisonings in Oslo: Epidemiology intention and follow-up. BMC Public Health 2012; 12: 858.

15 Cooper SA, Beaver W. A model to describe mild analgesic in oral surgery outpatients. Clin Pharmacol Ther 1976; 20(2)241-250.

16 'Some patients take 90 tablets of codeine-ibuprofen per day'. Australian Doctor, 14/11/2016, <http://www.australiandoctor.com.au/news/news-insight/>.

17 <https://www.tga.gov.au/database-adverse-event-notifications-daen>.

18 Frei MY, Nielsen S, Dobbin MDH, Tobin CL. Serious morbidity associated with misuse of over-the-counter codeine-ibuprofen analgesics: a series of 27 cases. Med J Aust 2010;193:294-296

19 Romach MK, Sproule BA, Sellers EM, Somer G, Busto UE Long-term codeine use is associated with depressive symptoms. J Clin Psychopharmacol 1999; 19: 373-376.

20 Dobbin M, Tobin C. Over-the counter (OTC) ibuprofen/codeine analgesics: misuse and harm. Victorian Department of Health, Melbourne. 2008. Available At:

<https://www.tga.gov.au/sites/default/files/scheduling-submissionpublic-submissions-scheduling-matters-referred-acms-15-august-2015-03.pdf>

In a 2016 study by Hotham and co-workers,²¹ the number of patients hospitalised due to serious adverse effects relating to misuse of OTC codeine-containing analgesics, and the related cost of hospitalisation, was determined for one South Australian hospital over a 5-year period. There were 99 admissions related to OTC codeine-containing analgesic (pertaining to 30 individual patients), with most relating to GI morbidities secondary to ibuprofen/codeine misuse. Patients consumed a mean of 28 codeine-containing tablets per day, over a mean duration of 606 days prior to admission. The mean cost per hospital admission was \$10,183.

Death

Substantial evidence from publications and case studies show that drug toxicity involving codeine contributes to both accidental and intentional deaths. Many of these deaths can be attributed to the misuse of combination codeine medicines.^{20, 22, 23, 24}

In 2013, Pilgrim *et al*²⁴ reported the outcome of Victorian coronial cases over a 10-year period from January 2001 to December 2011. There were 115 deaths in which codeine and ibuprofen were co-detected in post-mortem analyses or in which the misuse of codeine and ibuprofen was confirmed. In 7 of these deaths, NSAID-type pathology was recorded.

Roxburgh *et al* (2015)¹⁰ used data from the National Coronial Information System to examine trends in codeine-related deaths in all Australian states and territories between 2000 and 2013. It is likely that this data includes at least some of the data from Pilgrim *et al*.²⁴ Codeine-related deaths were defined as deaths where codeine was detected and codeine toxicity contributed to death, including deaths attributed to multiple drug toxicity (including codeine). Codeine toxicity was a contributory factor in 1437 deaths between 2000 and 2013. The underlying cause of death was determined to be codeine toxicity in 7.8% of cases (113 deaths), and multiple drug toxicity (including codeine) in 83.7% of cases (1201 deaths). Approximately 24% (343 cases) of the deaths were related to a prescription codeine product (usually Panadeine forte), 16% (229 cases) included an OTC codeine product, and in the remaining 60% of deaths, there was no information about whether the codeine consumed before death was prescribed or OTC. The toxicology profile in approximately half of the deaths also involved paracetamol, ibuprofen or doxylamine. Importantly, regardless of the source of codeine or its direct relationship with mortality, codeine-related deaths (with and without other drug toxicity) increased from 3.5 to 8.7 deaths per million persons between 2000 and 2009. Just under half of the deaths were attributed to accidental overdose, and the rate of these deaths also increased significantly by 9.3% each year, from 1.8 to 5.1 deaths per million persons.

In addition to morbidity and deaths associated with the misuse of combination products and opioid dependence, deaths have been reported in young children given codeine post-operatively and in babies of breast-feeding mothers given codeine. The risk of severe respiratory depression is much higher in children and *ultra-rapid* metabolisers because of the higher rate of conversion of codeine to morphine in these individuals.²⁵ Extensive metabolisers may have up to 30-fold

²¹ Mill D, Johnson J, Cook V, Monaghan E and Hotham E (2016), Abstract presented at Australian Professional Society on Alcohol and Other Drugs (APSAD), Sydney Conference. Abstract available here https://www.eiseverywhere.com/file_uploads/a5e36f68887d8c77c1a487a94559925b_20_DeannaMill.pdf

²² Ferguson L, Clarke I, Fisher A, Legg G, Batey R. Over the counter and into the grave: morbidity and mortality related to NSAIDS with codeine dependence. APSAD Conference 2010. Drug and Alc Rev 2010; 29 (Suppl. 1):2-82.

²³ McDonough MA. Misuse of codeine-containing combination analgesics. Medical Journal of Australia. 2011; 194: 486.

²⁴ Pilgrim J, Dobbin M, Drummer OH. Fatal misuse of codeine-ibuprofen in Victoria, Australia. Med J Aust 2013; 199(5):329-330.

²⁵ Zahari A, Ismail R. Review: Influence of cytochrome P450, Family 2, Subfamily D, polypeptide 6 (CYP2D6) polymorphisms on pain sensitivity and clinical response to weak opioid analgesics. *Drug Metabolism and Pharmacokinetics* 2014; 29: 29.

higher blood morphine concentrations than poor metabolisers, resulting in greater respiratory depression and sedation. In one study in 156 Caucasians given 25 mg codeine, ultra-rapid metabolisers had up to 45-fold higher concentrations of codeine metabolites than poor metabolisers.²⁶

The risks of respiratory depression, morbidity and death associated with codeine use in children under the age of 12 is of great concern, both internationally (US and the EU) and within Australia. Further, there is an increased risk of morbidity and death associated with codeine use in children under the age of 18 years, who have undergone tonsillectomy or adenoidectomy for sleep apnoea (see previous section).

A TGA literature search covering the period 2015 to 2016 has not found any clinical studies or systematic reviews of codeine safety published in this period. Other than the Roxburgh¹⁰ paper (discussed above under 'Death') which provides evidence of increasing rates of fatal codeine-related overdoses in Australia, no new codeine safety issues have been identified since 2015.

Dependence and addiction

Early reviews published in the 1970s and 1980s concluded that addiction²⁷ to codeine is rare.^{28, 29} However several other reports, including those published more recently, describe individuals who misuse or regularly use codeine.^{30, 31, 32, 33, 34} Anecdotal evidence suggests that some individuals may not be aware of a drug use problem until there are serious health harms (see 'Morbidity and death' above). It is this lack of awareness that highlights the need to educate consumers about the potential for codeine to cause dependency.

The risk of codeine abuse relates to the development of opioid dependence which causes significant social disadvantage. This stems from the need to acquire large quantities of OTC codeine-containing analgesics on a daily basis, and from the need to access opioid substitution therapy with methadone or similar drugs.

At a single drug dependence unit in South Australia, there has been a progressive increase in the annual incidence of codeine as the drug of dependence leading to a need for intervention, increasing from 31 in 2002-2003 to 174 by 2013-14.

In 2013, data from the national opioid pharmacotherapy statistics showed that codeine was the opioid drug of dependence for 1,038 clients receiving opioid substitution pharmacotherapy. Another recently published study of 902 people who inject illicit drugs, found that approximately one-third had also misused OTC codeine during the preceding six months.

²⁶ Yue QY et al. Quantification of the O- and N-demethylated and the glucuronidated metabolites of codeine relative to the debrisoquine metabolic ratio in urine in ultrarapid, rapid, and poor debrisoquine hydroxylators. *Ther Drug Monit* 1997; 19: 539-542.

²⁷ While dependence to opioids is predictable and can be managed by medication, addiction is abnormal and is classified as a disease manifesting in uncontrollable cravings and an inability to control drug use despite doing harm to oneself or others.

²⁸ Rowden AM, Lopez JR. Codeine addiction. *Ann Pharmacother* 1989; 23:475-477.

²⁹ Weppner RS. "Cheap Kicks": codeine cough syrup abusers and some of their social characteristics. *Int J Addict* 1971; 6:647-60.

³⁰ Busto UE, Sproule BA, Knight K, Romach MK, Sellers EM. Severe dependence on oral opiates. *Can J Clin Pharmacol* 1998; 5:23-28.

³¹ Sproule BAP, Busto UEP, Somer GM, et al. Characteristics of dependent and nondependent regular users of codeine. *J Clin Psychopharmacol* 1999; 19:367-372.

³² Dutch MJ. Nurofen Plus misuse: an emerging cause of perforated gastric ulcer. *Med J Aust*. 2008;188:56-57

³³ Kliner DJ, Pickens R. Indicated preference for drugs of abuse. *Int J Addict* 1982; 17:543-547.

³⁴ Nielsen S, Cameron J, Pahoki S. 2010. Over the counter codeine dependence: final report. Available at: http://atdc.org.au/wpcontent/uploads/2011/02/OTC_CODEINE_REPORT.pdf

Furthermore, the presence of codeine in OTC combination analgesics contributes to severe adverse outcomes associated with overdosage of the paracetamol³¹ or ibuprofen³⁵ component (see above 'Morbidity and death'). Anecdotally some abusers of OTC codeine medicines are consuming between 30 to 70 tablets or capsules per day of codeine-containing analgesics. A majority of people with codeine-dependent behaviours purchase their codeine-based medicines from multiple pharmacies.^{18, 36}

International regulation of codeine

Due to harm from abuse or misuse of codeine, including dependency and death, medicines containing codeine are specifically regulated in many countries. Regulatory controls include limits on pack sizes, label warnings on packaging, warnings in consumer information leaflets, and availability of codeine-containing medicines by prescription only.

United States of America (USA)

In the USA, under Food and Drug Administration (FDA) regulation all codeine products are available by prescription only. However some states follow an exemption (21 CFR 290.2) from prescription requirements for low-dose codeine mixed with a cough syrup, which may be dispensed by a pharmacist if the preparation contains not more than 200 mg codeine per 100 g of syrup and also includes one or more non-narcotic active ingredients.

In 2013, the FDA issued a warning that codeine is contraindicated in post-operative pain management of children under 12 following tonsillectomy and/or adenoidectomy, due to rare life-threatening adverse events or death, due to rapid metabolism of codeine to morphine.

In 2015, the FDA initiated a review into the possible risks of using codeine-containing medicines to treat coughs and colds in children less than 18 years of age because of the potential for serious side effects, including slowed or difficult breathing. This review is ongoing.

In addition, products containing codeine with paracetamol (acetaminophen) have black box warning labels regarding both hepatotoxicity and codeine metabolism:

Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 milligrams per day, and often involve more than one acetaminophen-containing product.

WARNING: Death Related to Ultra-Rapid Metabolism of Codeine to Morphine.

Europe and Asia

Medicines containing codeine are available only with a prescription in Hong Kong, Iceland, India, Japan, the Maldives, Romania, Russia, and the United Arab Emirates.

Of the 28 European Union (EU) member states (including the United Kingdom (UK)), 15 countries require a prescription (Austria, Belgium, Croatia, the Czech Republic, Finland, Germany, Greece, Hungary, Italy, Luxembourg, Netherlands, Portugal, Slovakia, Spain and Sweden), two countries permit OTC sale of cough linctus only (Hungary and Netherlands), and

³⁵ Robinson G. et al. Misuse of over-the-counter codeine-containing analgesics: dependence and other adverse effects. New Zealand Journal of Medicine 2010; 123: 59.

³⁶ Nielsen S, Cameron J, Pahoki S. 2010. Over the counter codeine dependence: final report. Available At: http://atdc.org.au/wpcontent/uploads/2011/02/OTC_CODEINE_REPORT.pdf

13 countries allow the sale of OTC codeine solid dosage forms.³⁷ Of the countries that permit codeine over the counter, all except Denmark require the sale to be under the supervision of a pharmacist. Five countries have limits on the quantity of tablets sold, and five countries contain a warning label relating to addiction on the pack. The permitted maximum allowable amount of codeine per preparation is 30 mg in Bulgaria, 20 mg in France, 15 mg in Poland, and 12.8 mg or less in the remaining countries.

Like the FDA, the European Medicines Agency (EMA) has issued recommendations to prevent the use of codeine-based preparations in children under 12 and to carefully consider the use of these medicines in children aged 12-18 years with breathing problems.

United Kingdom

Under the Misuse of Drugs Act and the Prescription Only Medicines (Human Use) Order 1997, there are provisions for small quantities of the controlled drugs, codeine and dihydrocodeine (DHC), to be available in non-prescription medicines in combination with non-opioid analgesics (paracetamol, aspirin and ibuprofen). They may include doses of up to 25.6 mg of codeine phosphate (i.e. 2 tablets/dose of 12.8 mg/tablet) and up to 14.92 mg of DHC tartrate (i.e. 2 tablets/dose of 7.46 mg/tablet). All non-prescription medicines containing codeine or DHC are classified as Pharmacy (P) medicines (equivalent to Schedule 3 in Australia).

Oral liquid products containing codeine for the symptomatic treatment of dry cough are also available with a prescription and classified as P medicines in strengths of up to 15 mg/5 ml. Before 2010 they were available in paediatric as well as adult formulations. Now they are available for use in adults over 18 years only.

In February 2005, following a review of the abuse and misuse of OTC medicines containing codeine or DHC, the MHRA implemented the following risk minimisation measures:

- Stronger warnings on the Summary of product characteristics (SmPC), Patient Information Leaflet (PIL) and label to reflect the importance of not taking the medicines for more than three days continuously without medical review, and to warn about the risks of addiction and headache from overuse.
- The PIL and labels state that products containing codeine can cause addiction if used continuously for more than three days. The outer pack is labelled '*For three days use only. Can cause addiction.*'
- Limiting the pack size to 32 tablets (4 days' supply) by voluntary agreements with companies, with any pack sizes available above 32 tablets labelled as '*dispensing only*'.
- Agreeing with companies, a responsible approach to promotional activities.

In July 2009, the Medicines and Healthcare products Regulatory Agency (MHRA) undertook a further review of risk minimisation measures in relation to codeine and dihydrocodeine-containing analgesics and implemented the following measures:

- Further strengthening the warnings on PILs, labels and advertising about the risk of addiction, the importance of not taking the medicine for more than three days consecutively and the need to seek advice from a doctor if painkillers are needed for longer than three days.
- Limiting the indications for non-prescription use to the short term treatment of acute, moderate pain which is not relieved by paracetamol, ibuprofen or aspirin alone.

³⁷ Foley M *et al.* The availability of over-the-counter codeine medicines across the European Union. Public Health, 2015, 129: 1465-1470.

- Removing all indications related to colds, flu, coughs and sore throats for OTC codeine.
- Reducing the pack size of all codeine and dihydrocodeine-containing non-prescription medicines, including effervescent forms to 32.
- Providing more information in the PIL about the signs and symptoms of addiction.

In 2010 the MHRA undertook a benefit risk review of OTC oral liquid cough medicines containing codeine, in children younger than 18 years. The review revealed a lack of robust evidence supporting the efficacy of codeine in treating cough in children. The conclusion was that the risks associated with OTC oral liquid medicines containing codeine for the treatment of cough outweighed the benefits in children and young people under 18 years. The following measures were implemented:

- the indication for children and young people under 18 years was removed from OTC oral liquid cough medicines containing codeine
- making it compulsory for all oral liquid codeine medicines to be supplied in child-resistant containers to minimise the risk of accidental ingestion by children
- updating of the packaging and leaflets for OTC liquid cough medicines that contain codeine to reflect the new advice that they are not for use in children and young people under 18 years.

A personal communication with MHRA in early 2016, indicated that there had been a drop in sales of OTC codeine combination analgesics in the UK post these regulatory reforms, however literature suggests that the UK has actually observed an increase in overall opioid use for pain management over the 2011-2013 period.³⁸

Canada

In Canada, under Section 36 of the Narcotic Control Regulations, products containing codeine are exempted from prescription if they:

- contain not more than 8 mg codeine in solid form; (for reference, in Australia Schedule 2 permits 10 mg or less, and Schedule 3 permits 12 mg or less) or
- not more than 20 mg codeine per 30 mL in liquid form and
- if the preparation contains at least two additional medicinal ingredients other than a narcotic.

In February 2016, all non-prescription codeine was banned in the province of Manitoba. Interestingly, in an online poll which asked whether other provinces should follow Manitoba's lead and switch low-dose codeine products to a prescription-only status, 79% said yes.³⁹ Some comments in response to this poll included:

- *'Most cases of opioid addiction start with abuse of xxx [OTC codeine-containing medicine]'*
- *'It is incomprehensible that we still have an opioid available for self-selection (with the approval of the pharmacist) when we are battling an opioid crisis. Low-dose codeine has next to no place in treatment and the risk of harm is much higher than any potential benefit' – Pharmacist*

³⁸ Berterame, S. *et al.* 2016 'Use of and barriers to access to opioid analgesics: a worldwide, regional, and national study.' *The Lancet* 387 (10028), 1644-1656.

³⁹ <http://www.canadianhealthcarenetwork.ca/pharmacists/magazines/pharmacy-practice/november-2016>

- *'As a Manitoba pharmacist, I think that the results have been very positive' – Pharmacist*
- *'These products gives the pharmacist an alternative when nothing else seems to work to relieve pain'*
- *'Needed for short-term emergency pain. Package offered for sale should be smaller'.*

In November 2016, a national report was released by the Canadian Institute for Health Information and the Canadian Centre on Substance Abuse.⁴⁰ The report provides figures on how often opioid overdoses, accidental or deliberate, send people to hospitals across the country and *'illuminates the toll of the escalating opoid crisis on the [Canadian] Health Care System'*.⁴¹

Summary of international regulation of codeine and implications for Australia

While the list of countries discussed above is not exhaustive, it is apparent that there is wide variability in the way codeine-containing medicines are regulated overseas. Furthermore, growing evidence suggests that countries with less strict regulations around codeine availability generally see more abuse and misuse of the low-dose OTC codeine medicines.^{37,42, 43, 44, 45}

⁴⁰ Canadian Institute for Health Information, Canadian Centre on Substance Abuse. *Hospitalizations and Emergency Department Visits Due to Opioid Poisoning in Canada*. Ottawa, ON: CIHI; 2016.

⁴¹ Howlett, K and Grant, K, 'Opioid poisoning puts more Canadians in hospital each year. Here's what Ottawa plans to do', The Globe and Mail, Posted online on 17 Nov 2016. Accessed on 24/11/2016, <http://www.theglobeandmail.com/news/national/how-opioid-poisonings-have-put-more-and-more-canadians-in-hospital-every-year/article32870508/>.

⁴² Razzaghi, E.M., Rahimi, A., Hosseni, M., and Madani, S. 1998-1999, 'Rapid situation assessment (RSA) of drug abuse in Iran (1998-1999)', Prevention Department, State Welfare Organization, Ministry of Health, I.R. of Iran and United Nations International Drug Control Program

⁴³ Paul, A., 'MDs seeing stream of opioid overdoses', Winnipeg Free Press, Posted on 17/11/2016. Accessed on 24/11/2016: <http://www.winnipegfreepress.com/local/mds-seeing-stream-of-opioid-overdoses-401671245.html>

⁴⁴ Gornall, J, 'Addicted to over-the-counter opium: Few realise codeine headache pills come from the same source as heroin - and evidence reveals more and more are getting hooked, Daily Mail Australia, Posted online 19/09/2016. Accessed 24/11/2016: <http://www.dailymail.co.uk/femail/article-2424740/Addicted-counter-opium-Few-realise-codeine-headache-pills-come-source-heroin--evidence-reveals-more-getting-hooked.html>

⁴⁵ A 100-a-day, over-the-counter addiction, Stuff Nation. Posted online 18/09/2016. Accessed 24/11/2016: <http://www.stuff.co.nz/stuff-nation/assignments/the-reality-of-dealing-with-addiction/10509686/A-100-a-day-over-the-counter-addiction>

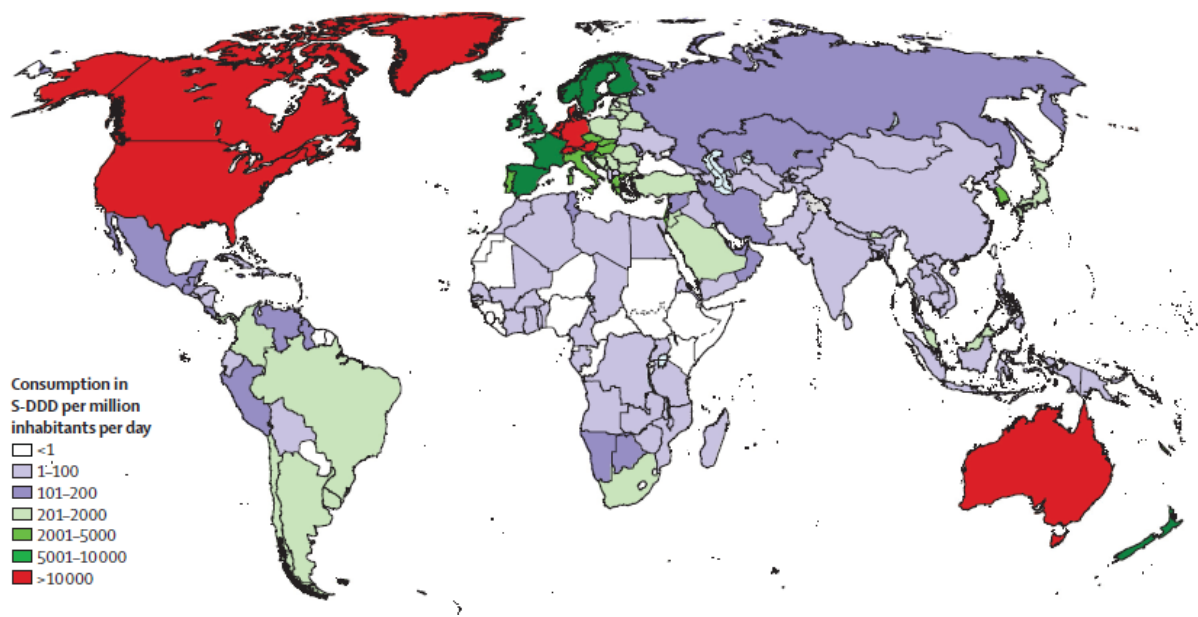


Figure 1: Mean availability of opioids for pain management in 2001-2013.³⁸

Concerningly for Australia, a recent 2016 study indicates that the use of opioid analgesics increased considerably over a decade (2001-2013), with Australia showing some of the most significant increases in opioid consumption for pain management behind Germany, North America, Austria and Gibraltar (Figure 1).^{38, 46} While the reasons behind this increase were not specifically identified in the study, authors speculated that physical availability, practical accessibility and affordability could be main driving factors.³⁸ This suggestion is not unreasonable given that Australia is in the minority of countries to sell codeine-containing medicines OTC.⁴⁷

Australian risk management framework

Standard for the Uniform Scheduling of Medicines and Poisons

Scheduling is a national classification system that enables states and territories to uniformly control how medicines and chemicals are made available to the public. Medicines and chemicals are classified into Schedules according to the level of regulatory control over the availability of the medicine or chemical required to protect public health and safety. The Schedules are published in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) and are given legal effect through state and territory legislation. The SUSMP is legally referred to as the [Poisons Standard](#).

Scheduling decisions are made by the Secretary of the Department of Health or their delegate according to subsection 52D(2) of the [Therapeutic Goods Act 1989](#) (TG Act) taking into account relevant matters of public health as set out under section 52E of the Act. These matters include the risks and benefits of the use of a substance, the purposes for which a substance is to be used, the substance's toxicity, dosage, formulation, labelling, packaging, presentation and any potential for abuse.

⁴⁶ Defined daily dose use per million people per day, where S-DDD = defined daily doses.

⁴⁷ Fitzpatrick, L 2016 'Is codeine too easy to get in Australia? These young addicts think so' Vice. Posted online 5 May 2016. Accessed 25/11/2016: http://www.vice.com/en_au/read/pharmaceutical-opioid-addiction-in-australia.

The [Scheduling Policy Framework \(SPF\)](#) is currently maintained by the Australian Health Ministers' Advisory Council (AHMAC) and provides the policy underpinning the mechanism for scheduling decisions. This policy guideline, together with the TG Act, sets out the scheduling process, guidance for amending the Poisons Standard, the classification system for medicines and chemicals, as well as guidelines for applications, public consultation and confidential information as these relate to scheduling applications.

The extensive public consultation associated with scheduling decisions and proposals to change the Poisons Standard is a critical component of this transparent regulatory framework to ensure that procedural fairness and natural justice are provided to those stakeholders that may be impacted by any scheduling decisions. In relation to codeine several calls for public submissions have been held in addition to those required by legislation.

Scheduling of medicines

Scheduling is the national classification system that controls how medicines and chemicals are made available to the public. Medicines and chemicals are classified into Schedules according to the level of regulatory control required to manage the availability of the medicine or chemical, and therefore protect public health and safety. The Schedules are published in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) and are given legal effect through state and territory legislation. The SUSMP is legally referred to as the [Poisons Standard](#).

Scheduling decisions take into account relevant matters of public health as set out under section 52(E) of the Act. These matters include:

- (1) In exercising a power under subsection 52D(2), the Secretary must take the following matters into account (where relevant):
 - (a) the risks and benefits of the use of a substance
 - (b) the purposes for which a substance is to be used and the extent of use of a substance
 - (c) the toxicity of a substance
 - (d) the dosage, formulation, labelling, packaging and presentation of a substance
 - (e) the potential for abuse of a substance, and
 - (f) any other matters that the Secretary considers necessary to protect public health.

In addition to the matters prescribed under subsection 52E (1) of the *Therapeutic Goods Act 1989* (above), the scheduling delegate must also consider the *factors* described in the SPF.

Scheduling factors

The Schedules and corresponding scheduling *factors* relevant to scheduling of codeine are described in the following sections. The factors are set out in the AHMAC Scheduling Policy Framework (SPF) document.

Schedule 2: Pharmacy medicines

1. The quality use of the medicine can be achieved by labelling, packaging, and/or provision of other information; however access to advice from a pharmacist is available to maximise the safe use of the medicine.
2. The use of the medicine is substantially safe for short term treatment and the potential for harm from inappropriate use is low. Suitable for diagnosis and treatment by the consumer in the management of minor ailments.

3. The use of the medicine at established therapeutic dosage levels is unlikely to produce dependency and the medicine is unlikely to be misused, abused or illicitly used. Medicines which do not meet this factor are not suitable to be classified as Schedule 2 Pharmacy Medicines, irrespective of any other applicable factors.
4. The risk profile of the medicine is well defined and the risk factors can be identified and managed by a consumer through appropriate packaging and labelling and consultation with a medical practitioner if required. There is a low and well-characterised incidence of adverse effects; interactions with commonly used substances or food and contra-indications.
5. The use of the medicine at established therapeutic dosage levels is not likely to mask the symptoms or delay diagnosis of a serious condition. Appropriate labelling and packaging can manage any risks.

Schedule 3: Pharmacist Only medicines

1. The medicine is substantially safe with pharmacist intervention to ensure the quality use of the medicine. There may be potential for harm if used inappropriately. The consumer can identify the ailments or symptoms that may be treated by the medicine but counselling and verification by a pharmacist is required before use. Pharmacist-consumer dialogue is necessary to reinforce and/or expand on aspects of the safe use of the medicine.
2. 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.
3. The risk profile of the medicine is well defined and the risk factors for adverse effects and interactions are known, identifiable and manageable by a pharmacist.
4. Where the medicine is intended for recurrent or subsequent treatment of a chronic condition, pharmacist intervention is required to monitor safe use of the medicine following recommendation by a medical practitioner or a pharmacist. The consumer may not be able to self-monitor the safe ongoing use of the medicine. The condition does not require medical diagnosis or only requires initial medical diagnosis, and the consumer does not require close medical management.
5. The use of the medicine at established therapeutic dosage levels may mask the symptoms or delay diagnosis of a serious condition. Pharmacist-consumer dialogue is required to detect the risk of masking a serious disease or compromising medical management of a disease, and to deal with it appropriately.

Schedule 4: Prescription Only medicines

1. The ailments or symptoms that the substance is used for require medical intervention. Diagnosis, management or monitoring of the medical condition is such that it requires medical intervention before the substance is used.
2. The use of the substance requires adjunctive therapy or evaluation. Adjunctive therapy could include other medicines, non-pharmacological measures, or specialised medicine delivery devices. Evaluation could include laboratory tests or additional clinical assessments.
3. The use of the substance at established therapeutic dosage levels may produce dependency but has a moderate propensity for misuse, abuse or illicit use. Control of access and duration of therapy by a medical, veterinary or dental practitioner is required.

4. The seriousness, severity and frequency of adverse effects are such that monitoring or intervention by a medical practitioner is required to minimise the risk of using the substance.
5. The margin of safety between the therapeutic and toxic dose of the substance is such that it requires medical intervention to minimise the risk of using the substance.
6. The seriousness or severity and frequency of the interactions of the substance (medicine-medicine, medicine-food, or medicine-disease) are such that monitoring or intervention is required by a medical practitioner.
7. The use of the substance has contributed to, or is likely to contribute to, communal harm. For example the development of resistant strains of microorganisms. Appropriate use, and/or the decision to continue treatment, requires evaluation by a medical practitioner.
8. The experience of the use of the substance under normal clinical conditions is limited. Unexpected effects of the substance may only become evident after widespread use. Close monitoring of the patient is required by a medical, veterinary or dental practitioner to monitor for unanticipated effects.

Schedule 8: Controlled medicines

1. The substance is included in Schedule I or II of the United Nations Single Convention on Narcotic Drugs 1961 or in Schedule II or III of the United Nations Convention on Psychotropic Substances 1971.
2. The substance has an established therapeutic value but its use, at established therapeutic dosage levels, is recognised to produce dependency and has a high propensity for misuse, abuse or illicit use.
3. The substance has an established therapeutic value but by reason of its novelty or properties carries a substantially increased risk of producing dependency, misuse, abuse or illicit use.

Current scheduling status of codeine

Codeine is currently listed in Schedules 8, 4, 3 and 2 of the [Poisons Standard](#) (see below), and thus has various controls and restrictions placed over its availability in order to protect public health. Low-dose codeine (8-15 mg/dose unit; Schedule 2 and Schedule 3) is currently available in cough and cold medicines and in combination with other analgesics OTC in pharmacies. High dose codeine (>30 mg/dose unit) and other opioids such as morphine, pethidine, tramadol and oxycodone are either available only by prescription (Schedule 4) or are controlled drugs (Schedule 8).

The schedule entries for codeine in the [Poisons Standard](#) are as follows:

Schedule 8

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

Schedule 4

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

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

except when included in Schedule 2 or 3.

Schedule 3

CODEINE when:

- a) not combined with any other opiate substance;
- b) compounded with one or more other therapeutically active substances, of which not more than one is an analgesic substance:
 - i) in divided preparations containing 12 mg or less of codeine per dosage unit; or
 - ii) in undivided preparations containing 0.25 per cent or less of codeine;
- c) labelled with a recommended daily dose not exceeding 100 mg of codeine; and
- d) in packs containing not more than 5 days' of supply at the maximum dose recommended on the label,

except when included in Schedule 2.

Schedule 2

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

- a) not combined with any other opiate substance;
- b) compounded with one or more other therapeutically active substances, of which at least one is phenylephrine and not more than one is an analgesic substance:
 - i) in divided preparations containing 10 mg or less of codeine per dosage unit; or
 - ii) in undivided preparations containing 0.25 per cent or less of codeine;
- c) labelled with a recommended daily dose not exceeding 60 mg of codeine; and
- d) in packs containing not more than 6 days' supply at the maximum dose recommended on the label.

Delegate's decision

The delegate's decision is primarily based on the protection of public health. The delegate considers advice from ACMS and all of the public submissions made in response to a public notice.

In making a decision to amend the Poisons Standard to protect public health, the delegate does not need to consider financial impacts to industry or the government. Often however, these considerations play a role in determining the implementation date for the scheduling decision.

Historical scheduling of codeine

The current scheduling of codeine in the Poisons Standard has been reviewed a number of times by the National Drugs and Poisons Schedule Committee (NDPSC) or the Advisory Committee on Medicines Scheduling (ACMS). The reviews were undertaken to follow up on concerns that have been raised regarding the abuse of codeine and the availability of all OTC combination analgesics containing codeine (e.g. paracetamol and ibuprofen products containing codeine).

Beginning in 2008, the NDPSC agreed to foreshadow a proposal (for consultation) to re-schedule all OTC codeine to Schedule 3 (with suggestions to limit the maximum daily dose to 100 mg codeine, limit the maximum pack size to 5 days' supply, restrict divided preparations to 12 mg of

codeine per dosage unit and restrict undivided preparations to 0.25% codeine). In addition, the Schedule 2 entry for combination products containing codeine, phenylephrine and other cough and cold products was considered appropriate (with an amendment to the maximum of 6 days' supply), if all other OTC codeine were included in Schedule 3. A Codeine Working Party assessed these proposals (which were considered at all subsequent NDPSC meetings until June 2009) when several amendments were made, including the up-scheduling of combination analgesics containing codeine (CACC) from Schedule 2 to Schedule 3. The implementation date was May 2010.

The final decision currently under consideration involved either making a change to the scheduling of codeine or leaving the scheduling unchanged. Either way, this decision will have an effect on multiple sectors of the community. To better understand the potential impacts of any codeine scheduling decision on stakeholders – including industry, consumers, government and healthcare professionals – the Department of Health is undertaking this Regulation Impact Review.

How effective were the scheduling changes for codeine in 2010?

Codeine-containing analgesics were up-scheduled in 2010 from Schedule 2 to Schedule 3; nevertheless, this change did not achieve the required reduction in harm to affected individuals.^{48,49, 50, 51, 52, 53, 54, 55, 56}

In recognition of the potential for harm arising from inappropriate use, the aim of this scheduling change was to provide increased surveillance of these medicines by a pharmacist to ensure quality use. Unfortunately, as indicated in the post 2010 health and safety reports (pp. 18 & 19), the re-scheduling has not been effective in reducing the adverse outcomes and opioid dependence. This therefore raises questions regarding the likely success of preventing further misuse and dependence of codeine-containing medicines by decreasing the pack size to 3 days supply and mandating warning statements on package labels. Changing the packaging of these medicines may not adequately address the problem of misuse and dependence; it may instead lead to a change in behaviour with dependent users sourcing codeine-containing analgesics elsewhere. Current labelling and packaging appear to be insufficient to warn individuals of potential adverse effects. As noted in the level of dependence, morbidity and deaths associated with codeine use (p. 16, *What are the health concerns with codeine use?*).

⁴⁸ Robertson CG *et al.* Beware of NSAID abuse: think twice before operating! ANZ J Surg: 2014; 84(6): 495-6.

⁴⁹ Australian Institute of Health and Welfare. National opioid pharmacotherapy statistics 2013, Drug treatment series no. 23. Cat. No. HSE 147. Canberra: AIHW: 2014:
<http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=60129547305>.

⁵⁰ Arora S, Roxburgh A, Bruno R, Nielsen S, Burns L. A cross-sectional analysis of over-the-counter codeine use among an Australian sample of people who regularly inject drugs. Drug Alcohol Rev. 2013 Nov; 32(6):574-81.

⁵¹ Page CB, Wilson PA, Foy A, Downes MA, Whyte IM, Isbister GK. Life-threatening hypokalaemia associated with ibuprofen-induced renal tubular acidosis. Med J Aust. 2011 Jun 6;194(11):614.

⁵² Ng JL, Morgan DJR, Loh NKM, Gan SK, Coleman PL, Ong GSY, et al. Life-threatening hypokalaemia associated with ibuprofen-induced renal tubular acidosis. Medical J Australia. 2011; 194:313-16.

⁵³ McDonough MA. Misuse of codeine-containing combination analgesics. Medical Journal of Australia. 2011; 194:486.

⁵⁴ Lake H. Ibuprofen belly: a case of small bowel stricture due to non-steroidal anti-inflammatory drug abuse in the setting of codeine dependence. Aust NZ J Psychiatry 2013; 47:1210-11.

⁵⁵ Waranilla Drug & Alcohol Services SA (DASSA) admissions data.

⁵⁶ Royal Adelaide Hospital admissions data.

Is the current scheduling of codeine best practice?

When considering the scheduling factors in the current SPF, together with the scientific information highlighting the public health concerns for rapid metabolisers of codeine, the codeine dependency that can result from therapeutic doses of codeine, and the significant health risks associated with the misuse of OTC medicines containing codeine, codeine clearly meets the criteria for a Schedule 4 (or higher) medicine.

In October 2015 the medicines scheduling delegate announced the interim decision to up-schedule all current Schedule 2 and Schedule 3 entries for codeine to Schedule 4 prescription only medicines. Due to extensive public comments, both in favour and opposed to re-scheduling, the delegate deferred making a final decision. Further public consultation was invited on several other options relating to the use of codeine.

The scheduling delegate sought public comment on a range of possible re-scheduling options on three occasions (see p. 92 *'Formal consultation periods regarding the re-scheduling of codeine'*). In general, the up-scheduling of codeine to prescription only is supported by submissions from pharmacists, many medical practitioners and their associated medical organisations. Submissions opposing up-scheduling of codeine largely came from OTC industry associations and individual pharmaceutical companies, the Pharmacy Guild of Australia (PGA) and a number of pharmacists and members of the public.

The specific reasons for the recommendation to up-schedule codeine includes matters relevant under section 52E of the TG Act (see p 28 *'Scheduling of medicines'*) and are outlined under the following headings:

- codeine as a prodrug and its metabolism;
- codeine toxicity and the availability of safer, more effective products;
- codeine use, misuse and abuse;
- current scheduling inconsistencies; and
- international scheduling considerations.

Each of these factors are detailed below.

Codeine as a prodrug and its metabolism

As a prodrug codeine causes direct toxicity primarily through its biotransformation into morphine. Metabolic polymorphism (as discussed on p. 14 *'What is codeine?'*) leads to major variability within the population in terms of the extent and speed 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 30 to 45-fold higher than those reached in poor metabolisers. High morphine plasma concentrations can lead to deep sedation, respiratory depression and death. This potential for severe adverse effects at therapeutic doses in ultra-rapid metabolisers suggests that codeine is an unsuitable OTC candidate. To limit excessive morphine concentrations following ingestion of recommended doses of codeine for any indication, some sources (including the Panadeine® product information packet) suggest that before taking codeine, the individual should know their particular CYP2D6 status. An individual would only know their CYP2D6 status after a specific blood test recommended or prescribed by their medical practitioner. Given that very few individuals are aware of their own metaboliser status, it would be very difficult to protect ultra-rapid metabolisers by way of label warnings.

Codeine toxicity and alternative products

Codeine shares the properties of other opioid analgesics (which are included in Schedule 4 or Schedule 8) and is potentially capable of producing dependence and in overdose, respiratory depression and reduced level of consciousness. There is also a greater risk of medication misadventure with codeine's relative lack of efficacy compared to safer products. From an efficacy perspective, there is no evidence that low-dose codeine combination analgesics provide any additional pain relief over optimal dosing of paracetamol, aspirin or ibuprofen (TGA Safety Review, March 2016 and references therein).

There are also a range of alternative analgesics for mild to moderate pain (e.g. Diclofenac/Voltaren or combination medicines such as ibuprofen plus paracetamol) that can fill the gap in the OTC market created by the re-scheduling of codeine. On the other hand, where strong pain relief is required, safer alternatives to codeine may be prescribed under doctors supervision. These may include medicines such as oxycodone or morphine, the correct doses of which can be accurately determined to manage pain due, unlike codeine, to their lack of metabolism variability *in vivo*.

Furthermore, reviews of the medical literature^{57, 58} and advice from Australian pain specialists indicate that OTC combination analgesics containing codeine plus either paracetamol or ibuprofen, show little or no additional analgesic benefit compared to analgesics without opioids (e.g. paracetamol, ibuprofen, other non-steroidal anti-inflammatories (NSAIDs), or aspirin).

Codeine use, misuse and abuse

As outlined in 'Analgesia' (p. 16), although the approved indication for Schedule 3 codeine products is for the *temporary relief of strong pain and discomfort associated with a number of different medical conditions*, the medical literature^{18, 59, 60, 61, 62, 63, 64, 65, 66, 67} and consumer submissions received in 2015 indicate that the use of Schedule 3 codeine products for long term relief of chronic pain is significant.

⁵⁷ Derry SM, Single dose codeine, as a single agent, for acute postoperative pain I adults. Cochrane Database Syst Rev 2009; 14; CD008099.

⁵⁸ 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; 21; CD001547.

⁵⁹ Robinson GM, Robinson S, McCarthy P, Cameron C. Misuse of over-the-counter codeine-containing analgesics: dependence and other adverse effects. NZ Med J.2010; 123:59-64.

⁶⁰ Sproule, B. A. P., & Busto, U. E. P., Somer, G. M., Romach, M. K. M. D., & Sellers, E. M. M. D. P. (1999). Characteristics of Dependent and Nondependent Regular Users of Codeine. Journal of Clinical Psychopharmacology, 19(4), 367-372.

⁶¹ Romach MK, Sproule BA, Sellers EM, Somer G, Busto UE Long-term codeine use is associated with depressive symptoms. J Clin Psychopharmacol 1999; 19:373-6.

⁶² Roussin A, Bouyssi A, Pouché L, Pourcel L, Lapeyre-Mestre M (2013) Misuse and Dependence on Non-Prescription Codeine Analgesics or Sedative H1 Antihistamines by Adults: A Cross-Sectional Investigation in France. PLoS ONE 8(10): e76499. doi:10.1371/journal.pone.0076499.

⁶³ Dutch MJ. Nurofen Plus misuse: an emerging cause of perforated gastric ulcer. Med J Aust. 2008; 188:56-7.

⁶⁴ Evans C, Chalmers-Watson TA, Gearry RB. Combination NSAID-codeine preparations and gastrointestinal toxicity. N Z Med J 2010; 123:92-3.

⁶⁵ Medani S, Short S, Wall C. Nurofen Plus toxicity—what should nephrologists be alert to? Rare complications of an increasingly misused medication. NDT Plus. 2010.

⁶⁶ Ferguson L, Clarke I, Fisher A, Legg G, Batey R. Over the counter and into the grave: morbidity and mortality related to NSAIDs with codeine dependence. APSAD Conference 2010. Drug and Alc Rev 2010; 29 (Suppl. 1):2-82.

⁶⁷ McDonough MA. Misuse of codeine-containing combination analgesics. Medical Journal of Australia. 2011; 194:486.

The genetic influence on the metabolism of codeine, and thus its risk versus benefit for some individuals is small, raising questions regarding the role of codeine in clinical practice. This suggests that an appropriately qualified practitioner should be involved with assessing risk before prescribing codeine. Rather than self-treating with long term OTC codeine-containing analgesics, the management of chronic pain would be better achieved through medical practitioner input, with advice on appropriate non-pharmacological treatments and alternative pharmacological treatments.

Current scheduling inconsistencies

There are significant inconsistencies in the restrictions on codeine availability between Schedules 2, 3, 4 and 8.

Codeine is available OTC as a Schedule 3 medicine (Pharmacist Only) in packs of up to 40 tablets (e.g. Panadeine Extra®) containing 15 mg each, totalling 600 mg codeine (in combination with paracetamol) per pack.

Paradoxically, the same total pack quantity of 600 mg codeine (single active ingredient) is also available as a Schedule 8 (Controlled Drug) medicine in packs of 20 tablets containing 30 mg each. A Schedule 8 substance is recognised to have potential for abuse or addiction.

Similarly, an even higher quantity of 1500 mg codeine per pack is available as a Schedule 4 medicine (Prescription Only) in packs of up to 50 tablets (e.g. Panadeine Extra®) containing 30 mg each (in combination with paracetamol) per pack.

The availability of codeine-containing medicines in the lower schedules of 2 and 3 of the Poisons Standard is also inconsistent with the known risk of developing codeine dependence associated with these medicines. Codeine dependency is a major public health concern, that in some cases requires opioid substitution therapy with methadone or similar drugs to overcome dependence (see previous section '*Codeine use, misuse and abuse*'). The intentional misuse and abuse of codeine leads to the ingestion of excessive doses of the companion drugs (usually paracetamol or NSAIDs) resulting in morbidity and/or death.^{31, 68}

International scheduling considerations

See '*International regulation of codeine*' above.

Regulatory options

Substances can either be up-scheduled or down-scheduled on application to the Secretary (or scheduling delegate). Re-scheduling applications may be submitted by the general public, industry or state and territory authorities.

An application to up-schedule codeine was made to the Secretary (or the Secretary's medicines scheduling delegate (the Delegate)) who sought advice on the proposed amendment from the Advisory Committee on Medicines Scheduling (ACMS) and an independent external evaluator. Additionally, the Delegate will also consider all public submissions received regarding how codeine should be made available to the Australian public.

Due to the significant health risks associated with OTC codeine-containing medicines (as outlined in the preceding sections as well as in the original scheduling application) and to ensure that public health and safety is protected using best practice regulation, the Department of

⁶⁸ Robinson G. et al. Misuse of over-the-counter codeine-containing analgesics: dependence and other adverse effects. *New Zealand Journal of Medicine* 2010; 123: 59.

Health, through the TGA, is currently reviewing OTC access to codeine-containing medicines in Australia.

What are the regulatory options and scenarios being considered?

The interim decision in October 2015 was to up-schedule all Schedule 2 and Schedule 3 codeine preparations to Schedule 4. In December 2015, the delegate considered other regulatory options such as restricting pack size and labelling. The final proposed options are summarised in Table 1.

Table 1: Summary of regulatory options

Option 1	The current scheduling of codeine remains appropriate.
Option 2	The current Schedule 2 entries for codeine in cough and cold medicine preparations be amended to reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction.
Option 3	The current Schedule 2 entries for codeine in cough and cold medicine preparations are up-scheduled to Schedule 3, and that the pack size is reduced to not more than 3 days' supply and include a label warning that codeine can cause addiction.
Option 4*	Up-schedule the current Schedule 2 entries for codeine to Schedule 4 and amend the current Schedule 4 and 8 entries: this forms part of the interim decision.
Option 5	The current Schedule 3 entries for codeine (including, but not limited to codeine-containing analgesics) is amended to reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction.
Option 6*	Up-schedule the current Schedule 3 entries for codeine to Schedule 4 and amend the current Schedule 4 and 8 entries: this forms part of the interim decision.

* The current interim decision consists of Option 4 plus Option 6.

Unless Option 1 is chosen, the scheduling decision is likely to be a pair of options (a scenario) selected from Options 2 to 6. In effect, the options could result in the four different scenarios summarised in Table 2.

Table 2: Summary of scenarios

Scenario 1 (Option 1)	No change to the status quo.
Scenario 2 (Options 2 and 5)	<p>Schedule 2 and Schedule 3 entries for codeine (including, but not limited to, cough and cold medicine preparations and codeine-containing analgesics) is amended to reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction.</p> <p><i>Summary:</i></p> <p>- Reduce pack size and include warning label for Schedule 2 and Schedule 3</p>

Scenario 3 (Options 3 and 5)	<p>The current Schedule 2 entries for codeine in cough and cold preparations is up-scheduled to Schedule 3. All Schedule 3 entries (i.e. those currently Schedule 3 and those previously Schedule 2) for codeine (including, but not limited to, cough and cold medicine preparations and codeine-containing analgesics), be amended to reduce the pack size to not more than 3 days' supply, and include a label warning that codeine can cause addiction.</p> <p><i>Summary:</i></p> <ul style="list-style-type: none"> - Schedule 2 up-scheduled to Schedule 3 - Reduce pack size and include warning label for Schedule 3.
Scenario 4* (Options 4 and 6) (interim decision)	<p>Schedule 2 and Schedule 3 entries for codeine (including, but not limited to, cough and cold medicine preparations and codeine-containing analgesics) be up-scheduled to Schedule 4.</p> <p><i>Summary:</i></p> <ul style="list-style-type: none"> - Schedule 2 and Schedule 3 up-scheduled to Schedule 4

* The current interim decision

To understand the impacts of any re-scheduling of codeine, the economic, social and regulatory impacts of the codeine scheduling options has been modelled. An important distinction between this RIS and those RIS' that are often associated with policy decisions, is that the scheduling delegate must consider the factors prescribed by subsection 52E of the Therapeutic Goods Act (the TG Act), and the scheduling policy framework (SPF) when making a scheduling decisions, and not necessarily the economic or social impacts of that decision.

Why are regulatory options being considered?

The above regulatory scenarios are being considered to protect public health and safety and discourage the abuse of medicines. The regulatory options are required because the current level of access to low-dose codeine products (as Schedule 2 and Schedule 3 products) do not provide the incentives for consumers to seek alternative treatment pathways that may provide better health outcomes.

To achieve better health outcomes for consumers, the following changes are required:

- Increased education to consumers and the community about the risks of misuse of low-dose codeine-containing medicines. During targeted stakeholder consultations, most stakeholders indicated that additional face-to-face education⁶⁹ for prescribers and pharmacists was unlikely to be necessary. With an estimated one million people using at least one Schedule 3 low-dose codeine medicine product a year, the need to invest in an education and awareness campaign, particularly for consumers is apparent.
- Increased awareness to consumers of the limited clinical information relating to incremental effectiveness of low-dose codeine in combination analgesics when compared to ibuprofen or paracetamol. That is, there is insufficient evidence to suggest that adding codeine to a

⁶⁹ Also known as 'Academic detailing', this is the process of delivering face-to-face education of prescribers by trained health care professionals, typically pharmacists, physicians, or nurses. The goal of academic detailing is to improve prescribing of targeted drugs to be consistent with medical evidence from randomized controlled trials, which ultimately improves patient care and can reduce health care costs.

medicine will increase its effectiveness as a pain reliever compared to paracetamol or ibuprofen alone.

- To encourage an appropriate level of medical intervention and oversight when codeine-containing medicines are required for particular health conditions (e.g. cancer pain).
- Discourage the use of low-dose codeine analgesics for chronic pain relief.
- To encourage exploration of alternative treatment or referral pathways (non-pharmacological pain management etc.) for chronic conditions.
- To encourage the use of safer analgesics (paracetamol and/or ibuprofen) in the first instance, even for strong pain relief.
- To promote a change in consumer purchasing behaviour in relation to low-dose codeine-containing medicines such that consumers do not inadvertently self-treat serious conditions with medicines that are ineffective for such a purpose (e.g. cough suppressant for chronic pain).
- To promote the quality use of medicines with the appropriate level of medical oversight, either through greater number of more frequent use of pharmacists consultations and GP oversight

Real-time monitoring programs

There is no provision in the *Therapeutic Goods Act*, Regulations (Part 6, Division 3A) or the SPF that allows for a real-time monitoring (RTM) system to be mandated as part of the delegate's scheduling decision. However, for the purpose of attempting to minimise the abuse and misuse of codeine-containing medicines, it is possible that a mandated RTM could be considered by the commonwealth, state and territory governments.

The Self Medication Association of South Africa (SMASA), the Community Pharmacy Sector and the Pharmacy Society of South Africa (PSSA), launched the real-time monitoring system known as the Codeine Care Initiative (<http://selfcare247.co.za/247-codeine-care-initiative/>) in 2013. In November 2016, an update on this initiative was provided to the TGA by SMASA. One key point that came out of this update was that the program was limited by a lack of universal adoption throughout the country. This was largely driven by operational limitations, as not all public hospitals have access to computerised record keeping.⁷⁰ This appears to be the only RTM program associated with codeine identified overseas.

If Australia was to mandate a RTM program for codeine, this would be inconsistent with Australia's national scheduling framework, as no such RTM programs currently exist for Schedule 4 (prescription medicines) or Schedule 8 (controlled drugs) medicines despite the higher risks associated with these medicines.

In 2005, a RTM program known as Project STOP commenced as an initiative of The Pharmacy Guild of Australia (PGA) and sought to prevent diversion of products containing pseudoephedrine for preparation of illicit drugs (predominately methamphetamine). This RTM program's aim was to monitor diversion rather than to prevent morbidity associated with high risk medicines.

⁷⁰ Personal communication, D Bayever

MedsASSIST program

The Pharmacy Guild of Australia (PGA) has rolled out a new voluntary real-time monitoring program called MedsASSIST. This system, which captures OTC codeine product sales information, involves a pharmacist-consumer consultation whereby the therapeutic need of a codeine medicine for the individual patient is assessed by the pharmacist. Furthermore, pharmacists ask for ID and seek consent to record the ID number in the system. If the patient does not consent to providing an ID, the pharmacist may choose not to supply the medicine. The pharmacist also records the name and the quantity of the requested codeine medicine and reviews any previous purchases of codeine medicine. If the pharmacist decides it is not therapeutically appropriate to supply a codeine medicine, they will explain the reason for this decision and may provide further clinical information or recommendations to support the patient's health. This will also be recorded in the system. The system does not prevent sales of OTC codeine-containing products, but incidents of where sales have been made under duress are recorded.

Since the introduction of MedsASSIST in February 2016, and as of 23 November 2016, approximately 68% (3810)⁷¹ of pharmacies across Australia have adopted the monitoring system, with over 2.7 million OTC codeine transactions recorded. The results of the MedsASSIST program have been periodically presented by the PGA to the TGA and ACMS during 2016 (Table 3).

Table 3: Results of PGA's MedsASSIST program

Parameter/Report Date	July 2016	September 2016
Data collection period	8 Feb – 14 July 2016	8 Feb – 13 Sept 2016
No. of pharmacies/No. of transactions	3413 (62%)/1,573,471	3652 (65%)/2,728,904
Average transactions/pharmacy	461	747 (+38%)
Number of unique ID numbers	796,850	1,313,709
ID appears once/more than once	72%/28%	66%/34%
ID appears 2-3 times (numbers)	20% (160,641)	22% (288,970)
ID appears more than 3 times (numbers)	8% (62,896)	12% (153,037)
Data analysis period	8 Feb - 30 June 2016	8 Feb - 6 Sept 2016
Number of transactions analysed	1,328,545	2,601,353
Number of denials	30,416 (2.29%)	51,247 (1.97%)
Number of safety sales*	12,603 (0.95%)	24,115 (0.93%)
Number of sales due to staff safety concern (this is a subset of safety sales)	756 (0.06%)	1447 (0.06%)

* Reasons for safety sales include 'patient risk inconclusive', 'patient distressed', and 'staff safety'

An overview of the MedsASSIST data:

- 62% (June 2016), 65% (September 2016) and 68% (November 2016)⁷¹ of all pharmacies are using MedsASSIST across various geographical locations (both city and rural pharmacies).⁷²
- Between July and September there was a 38% increase in the number of transactions recorded per pharmacy with only a 3% increase in the number of pharmacies participating in the program. Despite the increase in the number of transactions between July-September (38%), no increase in the level of denial was recorded.
- Between 8 February and 6 September 2016 (7 months), over 2.6 million transactions were recorded.⁷³ During this period:

⁷¹ Guild calls for codeine monitoring laws. Posted online 23 Nov 2016, Pharma In Focus 23, Issue date 21-27 Nov. <http://www.pharmainfocus.com.au/news.asp?newsid=11384>

⁷² Figures from June 2016 and September 2016 were provided to the TGA by the PGA directly.

- Over 97% of transactions were for a Schedule 3 combination analgesic product; the remaining were for Schedule 2 cold and flu products.
- Approximately 2% of transactions were denied.^{71, 72}
- Approximately 0.06% of transactions were made under duress in pharmacies (following a real or perceived threat to the safety of pharmacy staff).
- 66% of patients requested a codeine product once, while 12% requested a codeine product more than three times
- The most recent November 2016 figures suggest the number of recorded transactions has risen to 4 million transactions since March 2016.⁷⁴ During this period:
 - 86% of consumers who had made five or more purchases were recommended to seek medical advice with regards to managing pain, abuse and misuse.⁷⁴

Where a unique ID appears more than 3 times (within 7 months), it is likely that the person is dependent on codeine and therefore at risk of serious morbidity. As of September 2016, this number is 153,037 individuals.⁷² It is also noted that this number does not include the 35% of pharmacies who were not participating in the MedsASSIST program, and that codeine-dependent consumers are likely to seek out these pharmacies to obtain a supply of codeine products.

For the July 2016 period, there were a significant number of occasions when a consumer was denied a codeine product by a particular pharmacy,^{71, 72} but the data also highlighted that shopping at a second pharmacy subsequently allowed the individual to access codeine.⁷¹ One example provided to TGA during the consultation process showed that an individual received 660 tablets over the period despite their purchasing behaviour being tracked in MedsASSIST. This brings into doubt whether MedsASSIST is actually deterring consumers with codeine-dependence problems from accessing codeine, with the data suggesting that consumers with addiction problems will change their behaviour in order to source codeine. Some GPs and specialists have expressed concerns around the effectiveness of RTM.⁷⁵

Furthermore, the following issues have been raised by independent experts of the ACMS (Advisory Committee and Medicine Scheduling) or Australian Medical Association (these experts are qualified pharmacists, medical practitioners or other health professionals):

Given the instances of '*pharmacy shopping*' to source codeine,⁷⁶ questions have been raised whether the patient use of codeine is best monitored by general practitioners noting their ability to better diagnose, treat and manage patient care in relation to chronic pain. Often general practitioners are familiar with the available treatment options available for their patient, that may include any, or a combination of the following:

- Non-pharmacological treatment - pain management clinic, recommend exercise regime, stress or weight management; and/or

⁷³ More recent November 2016 figures given in a PharmaDispatch article (Pharmacy points to success of codeine monitoring. Posted online 23 Nov 2016 <https://pharmadispatch.com/news/pharmacy-points-to-success-of-codeine-monitoring>) suggests that this figure has risen to 4 million transactions.

⁷⁴ Pharmacy points to success of codeine monitoring. Posted online 23 Nov 2016, PharmaDispatch. No. 16 <https://pharmadispatch.com/news/pharmacy-points-to-success-of-codeine-monitoring>.

⁷⁵ Codeine monitoring 'too hard'. Posted online 11 Nov 2016, Pharma in focus, 7-13 Nov 2016. <http://www.pharmainfocus.com.au/Newsprint.asp?newsid=11340>

⁷⁶ Fitzpatrick, L 2016 'Is codeine too easy to get in Australia? These young addicts think so' Vice. Posted online 5 May 2016. Accessed 25/11/2016: http://www.vice.com/en_au/read/pharmaceutical-opioid-addiction-in-australia.

- Other non-opioid pharmacological interventions such as ibuprofen, paracetamol as well as sumatriptan or rizatriptan for migraine.

GPs also have the ability to refer patients to pain management specialists or clinics for greater oversight and intervention, a formal referral system that is not available for pharmacists.

- While MedsASSIST aims to provide pharmacists with a purchasing history for codeine-containing medicines, reservations were expressed relating to the limited ability of pharmacists to actively engage with 'challenging' patients to manage the use of codeine in OTC medicines, noting that the pharmacy environment does not usually allow for private conversations in the way that doctors' rooms do.
- States and territories will need to agree to support MedsASSIST with mandatory reporting; such changes require uniform adoption at the jurisdiction level and changes to relevant jurisdiction legislation, which would take time.
- Also questioned is whether a recording and monitoring system is consistent, in principle, with an OTC medicine (Schedules 2 and Schedule 3). Previous review of Schedule 8 (drugs of dependence) restrictions has recommended the use of Electronic Recording and Reporting of Controlled Drugs (ERRCD), a nationally consistent recording system for capturing all transactions involving Schedule 8 medicines in line with mandated state and territory requirements. ERRCD has not been implemented to date.

Regulatory and health economic impact models

A regulatory costing model and an economic and social impact model (health economic model) have been developed by an independent consultancy (KPMG). Each model was informed by a range of data sources, including public submissions, scientific literature, information provided by other government agencies, as well as industry and peak body consultations.

To determine and test the assumptions of the regulatory impact and economic impact models, data were sourced from the following relevant business units in the Department of Health:

- *Pharmaceutical Benefits Scheme (PBS)*. Potential increased costs due to additional prescription of PBS listed medicines in the case of up-scheduling to Schedule 4.
- *Medicare Benefits Schedule (MBS)*. Increased costs due to additional medical practitioner visits to obtain prescriptions in the case of up-scheduling to Schedule 4.

Primary data sources are referenced throughout, and include:

- Australian Register of Therapeutic Goods (ARTG, August 2016): product name, formulation, sponsor (company) and manufacturer details of all therapeutic goods lawfully supplied in Australia
- IMS Health (June 2013): product sales data
- Pharmaceutical Benefits Scheme (PBS, August 2016): details of the medicines subsidised by the Australian Government
- Medicare Benefits Schedule (MBS, August 2016): details of the Medicare services subsidised by the Australian Government

- Public submissions to the TGA (May 2015 – January 2016): from interested members of the public, individual specialists (i.e. pharmacists and medical practitioners), pharmaceutical companies, representative / peak bodies, and other agencies⁷⁷
- Confidential submissions to the TGA (May 2015 – January 2016, supplied by TGA): submissions as above, but not permitted for public release
- Interviews (August 2016): see '*Overview of consultation activities*' (p. 91) for more detail
- MedsASSIST (PGA, 10 August 2016): the real-time recording and monitoring program established by the PGA to support patient safety and improve the clinical outcomes for medicines containing codeine
- Published scientific literature concerning health effects of long-term codeine use, and the comparative effectiveness of pain relief compared to Paracetamol and ibuprofen.

Regulatory impact model

The development of the regulatory model was undertaken in accordance with the Office of Best Practice Regulation (OBPR) Guidance.⁷⁸ As outlined in this framework, regulatory costs were estimated for administrative compliance costs and substantive compliance costs only. Delay costs (application and approval delays) were determined to be out of the scope of the model as it was envisaged that any changes to scheduling for codeine products would incorporate sufficient time for industry to respond without experiencing any stock-outs (which occur when existing pharmaceutical stock is withdrawn or exhausted prior to new stock being available).

The model identified the key regulatory compliance processes that would arise from the implementation of each option. Component elements of each of the identified regulatory processes were then broken down into their respective time, cost and frequency components and the value of the respective inputs sourced from previous regulation impact statements prepared by the TGA, as well as information provided via consultations with industry and peak bodies. Cost models were developed in Microsoft Excel, with the summary for each option also presented in the standard Regulatory Burden Measure (RBM) format.

Inputs and assumptions

The development of the regulatory cost estimates was informed by targeted consultation with sponsors who currently produce codeine-based products in the OTC market. The target sponsors were Sandoz Pty Ltd, Sanofi-Aventis Australia Pty Ltd, GlaxoSmithKline Consumer Healthcare Pty Ltd, Soul Pattinson Manufacturing Pty Ltd and Johnson & Johnson Pacific. These companies occupy both distinct and overlapping segments of the OTC and prescription market and were able to provide a range of perspectives given the different incentives and risks that are intrinsic to their business models.

Sponsors were provided with a list of questions ([Appendix A](#)) which were subsequently used to structure conversations in meetings and focus on issues directly related to the modelling and implementation implication of the different options.

Broadly, the interviews were structured around six topics outlined in the questionnaire:

- product strategy

⁷⁷ See Therapeutic Goods Administration website for all publicly available submissions:

<https://www.tga.gov.au/scheduling-submission/public-submissions-scheduling-matters-referred-acms-15-august-2015>

⁷⁸ '*Regulatory Burden Measurement Framework*' dated February 2016

- market response
- labelling
- packaging
- updated listing and regulatory approvals
- implementation.

The baseline assumptions used to support the regulatory model are reported in Table 4, p. 45.

Business-as-usual (BAU) variations to existing medicines

There is high variability between how often sponsors change an aspect of their product (e.g. update label, Product Information (PI) etc.). Some sponsors vary their ARTG entry regularly (even more than once a year), whereas other sponsors will not vary their products for several years. The majority of ARTG variation applications are for prescription products.

- A 2014 survey of industry revealed that companies will update their labels as part of BAU, on average, every 3 years.⁷⁹ Therefore, with an assumed 18 month implementation timeframe which also aligns with the RASML implementation cycle, it is assumed that at least half of the affected sponsors will have the opportunity to roll the labelling changes into already scheduled updates.
- Consultations with sponsors and manufacturers have identified the cost of implementing a minor labelling change ranges between \$2,000 and \$6,500 per product. This incorporates the costs of artwork and internal processes to quality assure and implement the change on the production line. For the purposes of the costing, drawing from the TGA RIS on General Requirements for Labels for Medicines, the average cost to implement a labelling change (per OTC product) is estimated at \$4,171.⁸⁰ We have assumed that this incorporates the aspects of multiple labels per product.
- These minor label change costs include pre-production costs (such as label redesign and approval, artwork and proofing) and production costs (new printing plates for conventional printing processes, changes to the digital printing process). The costs also cover any potential changes to the Product Information (PI)/ Consumer Medicines Information (CMI).
- A minor label change is defined as a small change to the phrasing of text on a label that does not necessitate a change to, or rearrangement of, other label graphics.

Regulatory costs associated with any transition

- The compliance costs for stock recalls has not been estimated as the assumed implementation timeframe should provide adequate time for turn-over of stock across the supply chain. PGA have indicated that the codeine products have a short shelf life (i.e. rapid turnover) within pharmacies⁸¹ due to fast sales associated with these products.

⁷⁹ TGA, Regulation Impact Statement: General Requirements for labels for medicines, <https://ris.govspace.gov.au/files/2016/08/General-requirements-for-labels-for-medicines-RIS.pdf>, July 2016.

⁸⁰ TGA, Regulation Impact Statement: General Requirements for labels for medicines, <https://ris.govspace.gov.au/files/2016/08/General-requirements-for-labels-for-medicines-RIS.pdf>, July 2016, p.32.

⁸¹ Over 1 month, PGA personal communication, September 2016

- A default FTE wage rate of \$37.40 per hour and an on-cost multiplier of 1.75 have been adopted to account for non-wage labour on-costs as per OBPR guidance.⁸² This results in a scaled up rate of \$65.45 per hour.
- An individual's time has been costed at \$29.00 per hour as per OBPR guidance. A pharmacist's wage has been estimated at \$35.90 per hour⁸³ (therefore \$62.83 per hour when the on-cost multiplier of 1.75 is applied). A doctor's wage has been estimated at \$97 per hour⁸⁴ (therefore \$169.75 per hour when the on-cost multiplier of 1.75 is applied).
- The amendment of current Schedule 4 and Schedule 8 entries in the Poisons Standard will have administrative Government impact only (legislative change) but will not have any impact from a regulatory cost perspective on businesses, community organisations or individuals.

Baseline assumptions

Number of codeine products entered on the ARTG (as at August 2016)

Table 4 details the current distribution of codeine products across Schedule 2, Schedule 3, Schedule 4 and Schedule 8.⁸⁵

- Seventy-three (73) entries on the ARTG are for codeine products that currently have Annual Charge Exemption (ACE) status. This means they have \$0 turnover and are not being actively marketed in Australia. These entries have been excluded from Table 4.
- As some ARTG entries cover more than one medicine unit (e.g. different pack sizes), a multiplier has been applied to ARTG entries for each of the following types of medicines:
 - Prescription (Schedule 4) – 2.3 medicines per ARTG entry; and
 - OTC (Schedule 2 and Schedule 3) – 2.5 medicines per ARTG entry.⁸⁶
- The result of applying this multiplier is shown as the 'adjusted' value in brackets in Table 4.
- The ARTG data indicates the majority of products with codeine as an active ingredient within the Schedule 3 category. Furthermore, an analysis of sponsors with a product presence in multiple categories finds that:
 - all 15 sponsors with Schedule 2 products also have products in the Schedule 3 category;
 - of the 15 sponsors with Schedule 2 products, three also have products in the Schedule 4 and/or Schedule 8 categories;
 - of the 22 sponsors with Schedule 3 products, five also have products in the Schedule 4 and/or Schedule 8 categories; and

⁸² Office of Best Practice Regulation, 'Guidance Note: Regulatory Burden Measurement Framework', dated February 2016, p.18

⁸³ www.open.edu.au/careers/healthcare-medical-pharmaceuticals/pharmacists, Based on average salary of \$70,000.

⁸⁴ http://www.payscale.com/research/AU/Job=General_Practitioner/Salary (click on 'Show hourly rate' link).

⁸⁵ ARTG entries relating to codeine derivatives such as dihydrocodeine and norcodeine have been excluded from Table 4 as the re-scheduling decision relates only to products with codeine as an active ingredient. Similarly, listings for 'export only' products that contain codeine as an active ingredient have also been excluded as these are not regulated in accordance with the Poisons Standard.

⁸⁶ Sourced from a 2014 survey of companies and referenced in TGA, Regulation Impact Statement: International Harmonisation of Ingredient Names', v.1, dated November 2015, p.39.

- No sponsors have products across all four categories.
- For many medicines, there is more than one label associated with a product. For example, a medicine in a blister pack is assumed to be associated with two labels (the backing of the blister pack and the outside carton). Based on an analysis of ARTG entries, a multiplier is applied to the number of medicine products to estimate the number of associated labels:
 - Prescription – 1.89 labels per medicine product; and
 - OTC – 1.85 labels per medicine product.⁸⁷

Table 4: Number of products containing codeine phosphate [actual and (adjusted)] listed in the ARTG by Schedule

Sponsor	Number of products [actual (adjusted)] ^a				
	Schedule 2	Schedule 3	Schedule 4	Schedule 8	No. of ARTG entries
Alphapharm Pty Ltd	1(2.5)	5(12.5)	1(2.3)		7 (17.3)
Amneal Pharma Australia Pty Ltd		3(7.5)			3 (7.5)
Apotex Pty Ltd	9(22.5)	30(75)			39 (97.5)
Arrow Pharma Pty Ltd	2(5)	7(17.5)		1	10 (23.5)
Aspen Pharma Pty Ltd		14(35)	4(9.2)	1	19 (45.2)
Aspen Pharmacare Australia Pty Ltd			1(2.3)		1 (2.3)
Aurobindo Pharma Australia Pty Ltd		4(10)			4 (10)
Bayer Australia Ltd	2(5)	1(2.5)			3 (7.5)
Biotech Pharmaceuticals Pty Ltd	1(2.5)	3(7.5)		1	5 (11)
Care Pharmaceuticals Pty Ltd		2(5)			2 (5)
Cipla Australia Pty Ltd	2(5)	12(30)			14 (35)
Generic Health Pty Ltd	2(5)	7(17.5)			9 (22.5)
GlaxoSmithKline Consumer Healthcare Australia Pty Ltd	2(5)	7(17.5)			9 (22.5)
Johnson & Johnson Pacific Pty Ltd	5(12.5)	1(2.5)			6 (15)
Orion Laboratories Pty Ltd T/A Perrigo Australia	1(2.5)	5(12.5)			6 (15)
Pharmacare Laboratories Pty Ltd	5(12.5)	12(30)			17 (42.5)
Pharmacor Pty Ltd		6(15)			6 (15)
Phebra Pty Ltd				1	1
Reckitt Benckiser Pty Ltd		3(7.5)			3 (7.5)
Sandoz Pty Ltd	2(5)	3(7.5)			5 (12.5)
Sanofi-Aventis Australia Pty Ltd		8(20)	4(9.2)		12 (29.2)

⁸⁷ TGA, Regulation Impact Statement: International Harmonisation of Ingredient Names', v.1, dated November 2015, p.39.

Sponsor	Number of products [actual (adjusted)] ^a				
	Schedule 2	Schedule 3	Schedule 4	Schedule 8	No. of ARTG entries
Sigma Company Limited	4(10)	11(27.5)			15 (37.5)
Soul Pattinson Manufacturing Pty Ltd	4(10)	10(25)			14 (35)
Symbion Pty Ltd	4(10)	14(35)			18 (45)
Total ARTG entries [actual (adjusted)]	46 (115)	168 (420)	10 (23)	4 (4)	228 (562)
Actual ARTG entries affected (%)	20	74	4	2	
No. of sponsors affected (n=24)	15	22	4	4	
Sponsors affected (%)	63	92	17	17	

^a Note not all columns will sum due to rounding; Source: ARTG extract 1 August 2016.

Health economic impact model

This part of the document provides an overview of the health economic model. More information is available in the KPMG Report (Annex 1) which provides clear illustrations of the potential sources of bias in the analysis and how these were resolved.

How the health economic model works

The health economic model works in five main steps, as follows:

Step 1: Simulation. The simulation is based on holding constant the total amount of codeine currently used by each of the five patient/consumers groups (see '*Five Groups of Consumers*' p. 51) (though possibly in different pack sizes) and then adjusting the variables including the following to reflect the post-regulatory change environment:

- packs of low-dose codeine
- out of pocket cost
- pharmacy purchases
- GP consultations.

Step 2: Plausibility analysis. The next step assesses, for each consumer group, the plausibility that this change in consumer level resource use will occur (holding the consumption of low-dose codeine constant) when considered relative to alternative pathways. Each of these alternative pathways has different uses of resources and health outcomes associated with them. The proposed regulatory change does not add pathways; it removes one and hence changes which of the existing pathways that patients will take. These alternative pathways will often incorporate discussions with both GPs and pharmacists, and include options such as:

- use of an OTC analgesic (e.g. paracetamol and/or ibuprofen) without codeine
- non-pharmacotherapy
- prescribed low or high dose codeine
- alternative prescribed pharmacotherapy
- GP or self-referrals to allied healthcare providers

- GP referrals to specialist pain clinics.

Step 3. Allocation of population across pathways. This step entails identifying the proportion of consumers in each group (cohort) that will pursue each pathway. This proportion varies across groups and also depends on factors such as the capacity for the existing pain clinics to see additional patients, including those who are referred by their GP and are eligible for a Medicare rebate.

Step 4. Determination of resource use and health outcomes. This step assigns changes in resource use to each cohort, where these changes in resource use and health outcomes are a consequence of changes in behaviour.

Step 5. Project changes over time. The final step projects these changes over the specified ten-year period, taking into account changes in cohorts, the ongoing needs for additional services and the longer term impact on health outcomes.

Sources of complexity – interdependency and data paucity

The *first source* of complexity in developing this model relates to the interdependency between the responses by the three main stakeholder groups for this model (consumers, GPs and pharmacists) to the proposed regulatory change. In summary, potential actions by these groups are:

- **Consumers** will need to decide whether they go to their GP, consider the treatment options provided by the GP, and/or use OTC non-codeine analgesics such as paracetamol and/or ibuprofen
- **GPs** will have a new patient group for whom they can suggest a range of additional options (appropriate for the patient), including referring patients to specialist pain units or allied healthcare providers; providing scripts of low or high dose codeine or other prescription only medicines; and/or suggesting OTC pain relief medications
- **Pharmacists** will continue to interact with consumers who are seeking pain relief, such as those who require prescription medications, some of which will be new to the consumer, and consumers continuing to attend the pharmacy seeking pain relief without any prescriptions for medications.

The *second source* of complexity was the paucity of data that could inform the estimate of the key benefit of the proposed regulatory change; that being the proportion of current users of OTC low-dose codeine will experience a health gain, including preventing deaths, as a consequence of this change. No data was available to inform the following estimates:

- the number of people who are currently dependent on low-dose codeine (note high dose specifically excluded)
- the number of adverse events attributable to low-dose codeine (excluding high dose codeine)
- the number of people who use low-dose codeine chronically and, while currently not dependent, are at risk of dependence.

The critical issue in developing the economic model is the combined effect of these two complexities (interdependency between responses and paucity of estimate data). Unless there are changes in treatment (the cumulative result of changes in activity and/or decisions made by the three groups identified above) there will be very limited changes in health outcomes. The proposed regulatory change in itself will not produce the expected benefits; rather, it will be the changes in people's activity and behaviour that realises the benefits.

The *first way* in which complexity described above is accommodated within the simulation model is by the use of five separate consumer groups, rather than relying on the concept of an 'average' consumer. This segmentation of the population allows the plausibility of responses to the proposed re-scheduling to be assessed more meaningfully and also reduces sources of unintentional systematic error that result from working with a model based on the characteristics of an 'average' consumer. However, this approach does increase the number of required assumptions, an important consideration in this data-poor area. A possible consequence of these additional assumptions is that a very wide range for any resultant metric, such as a net cost or benefit, emerges as a consequence of sensitivity analyses that use multiple variables. The model incorporates a set of analyses that identify the most plausible range of each parameter and interdependencies between parameter, before conducting the sensitivity analyses, hence addressing this risk.

The *second way* in which these complexities accommodated in the simulation model is its conservative approach to estimating the size of the projected benefits of the proposed regulatory change (See '*Sources of uncertainty*' below). This approach entails ensuring that the base case parameters for estimating these benefits is conservative, and that the key mechanisms by which this gain is achieved, as articulated by stakeholders, is clearly mapped to these explained. Potential losses in health outcomes to some consumers were also identified by stakeholders are also incorporated into the model.

Sources of uncertainty

In general, simulation modelling has two main types of uncertainty, those associated with model structure and those associated with model inputs. Further information regarding each uncertainty is described in the Annex 1 of this report (KPMG report – Annex E).

In this model the main drivers of input uncertainty are related to the potential health benefits. These are:

- the proportion of consumers that could potentially benefit from changing their pathway
- the proportion of consumers who will change their pathway in an optimal way
- the extent of additional health benefits that will be achieved if consumers with the potential to benefit change their pathway and receive improved treatment
- the time period that the health benefit is maintained without the need for additional investments in treatment and therapy.

As a general principle, the economic model sought to take conservative approaches to the estimation of health gains.

The main reason for this conservative approach was that health gains were the primary driver of benefits and also the most contested benefit (there was wide disagreement across various stakeholders); and for either case (low or high benefits), there was minimal supporting data and evidence.

As a general principle, the economic model sought to take conservative approaches to the estimation of health gains, for two reasons.

The first reason for taking a conservative approach was that the health benefits arising from the improved therapeutic pathways taken by patients who would otherwise be chronic users of low-dose codeine were the primary driver of benefits in the model, but are likely to be the most contested benefit. There was wide disagreement across the range of stakeholders as to the proportion of current chronic or acute users who would benefit from using different therapeutic pathways, and the extent of this benefit. Stakeholders who were supportive of the up-scheduling highlighted the benefits in terms of patients who would have an improved diagnosis of chronic or acute pain and also a shift to high dose codeine to reduce the risks related to paracetamol

and/or ibuprofen use. These stakeholders also referred to the evidence from the Cochrane⁸⁸ systematic reviews regarding the evidence of limited effectiveness of low-doses of codeine compared to paracetamol and/or ibuprofen alone. However, no stakeholder provided supporting evidence or data, other than the Cochrane reviews, and instead gave specific examples. Stakeholders in favour of the scheduling proposal gave specific examples of patients who suffered from migraines and were prescribed sumatriptan rather than codeine medications as a result of GP advice, or alternatively patients that suffered knee pain were referred to weight-loss clinics to better manage their specific symptoms. Stakeholders who were not supportive of the up-scheduling gave examples of patients (>65 years of age) who could not tolerate NSAIDs such as ibuprofen and would now have no options available to them.

The second reason for taking a conservative approach was that the protocol⁸⁹ to be applied to the valuation of a statistical life year is the use of an 'unconstrained' willingness to pay \$182,000. This statistical life year is intended to be a year at full health and therefore is also the value of a Quality Adjusted Life Year (QALY). The unconstrained willingness to pay approach is the preferred option under this protocol; however, it results in a much higher value being placed on a QALY compared to that used in health economics and health technology assessment in Australia and internationally.⁹⁰

Avoided deaths were an additional benefit. It was not possible to develop an accurate estimate of deaths that could be prevented as a consequence of Option 6. A published study provided an estimate of the annual deaths attributable specifically to OTC codeine medicines. However, the authors indicated that when deaths involving OTC codeine medicine abuse occurred, it was likely that there were multiple influencing factors and changed access to OTC codeine medicines would not necessarily prevent these deaths.¹⁰ The base case of the model assumed conservatively that 5 deaths would be prevented and this assumption was varied in the sensitivity analysis (see '*Sensitivity analyses*' p. 60).

Additionally, the only OTC low-dose codeine medicine specific data that was available to support the model (IMS data for sales of codeine-based products) was for 24 months to September 2013). An extrapolation of the IMS sales data was used to estimate the number of sales in 2017 (base year). Some externally sourced inputs (such as categorisation and fee structure for MBS GP consultations and the discount rate) were not specific to the options being modelled but

⁸⁸ Cochrane reviews are systematic reviews of primary research in human healthcare and health policy, and are internationally recognised as the highest standard in evidence-based healthcare resources. See <www.cochrane.org/whjat-is-cochrane-evidence>. Relevant reviews are: Derry S, Moore RA, McQuay HJ. Single dose oral codeine, as a single agent, for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2010, Issue 4. Art. No.: CD008099. DOI: 10.1002/14651858.CD008099.pub2. Toms L, McQuay HJ, Derry S, Moore RA. Single dose oral paracetamol (acetaminophen) for postoperative pain in adults. Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD004602. DOI: 10.1002/14651858.CD004602.pub2. Derry CJ, Derry S, Moore RA, McQuay HJ. Single dose oral ibuprofen for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD001548. DOI: 10.1002/14651858.CD001548.pub2. Toms L, Derry S, Moore RA, McQuay HJ. Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD001547. DOI: 10.1002/14651858.CD001547.pub2. Derry S, Karlin SM, Moore RA. Single dose oral ibuprofen plus codeine for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2015, Issue 2. Art. No.: CD010107. DOI: 10.1002/14651858.CD010107.pub3. Derry CJ, Derry S, Moore RA. Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD010210. DOI: 10.1002/14651858.CD010210.pub2.

⁸⁹ Office of Best Practice Regulation, 'Best Practice Regulation Guidance Note: Value of statistical life', dated December 2014.

⁹⁰ The Pharmaceutical Benefits Advisory Committee does not declare its valuation of A QALY but it is likely to be in the order of \$50,000 per QALY. For a discussion of the theory and practice of choice of valuation of a QALY and the use of a shadow price in cost benefit analysis, see Brita A.K. Pekarsky, *The new drug reimbursement game; A regulator's guide to playing and winning*, Springer, 2015.

rather relate to the broader health system. Initial assumptions were formed for the remaining inputs and then, in the absence of data or relevant literature, they were tested during interviews with peak bodies (i.e. expert opinion was sought).

Five main considerations for economic model

Listed below are five key considerations that the model addresses and which collectively reduce the systematic bias that may arise from a simpler ‘average-consumer’ model. These considerations are:

- Why is the concept of an ‘average’ consumer potentially misleading?
- At what point does using an ‘average’ response to the proposed regulatory change produce a biased estimate of the increase in GP visits?
- What are the five consumer groups and what are their differences?
- What are the drivers of the model’s benefits and costs? and
- How are the model’s key parameters determined?

Is there an average consumer of codeine?

To test the extent of any systematic bias that could emerge if the economic model were based on an average consumer rather than differentiated groups of consumers, a “pre-modelling” exercise using hypothetical data was constructed. Table 5 shows the average use of codeine per customer, which was derived for hypothetical sales data associated with products in the market (Table 4, p. 45). Considering a market with 14 million sales and 1.1 million consumers, the average use per consumer is 12.7 packs per year. From interviews with stakeholders, there appears to be at least two broad types of consumers. First, acute users, who were assumed for this pre-modelling exercise to use an average of two packs per year. Second, chronic users who were assumed for this exercise to use an average of 120 packs per year (two to three packs a week). When these patterns of use are combined with the total number of consumers and total volume used, then it is possible to solve for the proportion of users in each groups. In this hypothetical case, chronic users represent 9% of the market and 86% of the sales.

Table 5: Consumer share of market and share of sales by two hypothetical consumer groups

	Low use consumers	High use consumers	Total use
Number of consumers	1,000,000	100,000	1,100,000
Packs per consumer per year	2	120	12.7
Packs per year	2,000,000	12,000,000	14,000,000
Share of consumers	91%	9%	100%
Share of packs	14%	86%	100%

Source KPMG report Table E1

The implications for the economic modelling are as follows:

- Historical information and experience suggests that a different behavioural response in the high use consumer compared to the low use consumer when regulatory changes are made that place tighter restrictions on availability. If schedule 2 and 3 medicines were up-

scheduled to schedule 4 requiring all codeine-containing medicines to be prescribed by a medical practitioner only, then following implications are likely:

- The demand for the medicines by the low use consumer may reduce use if required to take time to see a GP and possibly the incur the additional cost of the co-payment.
- The high use group may be willing to visit a GP 12 times a year, but they are far less likely to make 50 visits per year.
- Large changes in the behaviour of a small group of consumers, the 9% with high use, will lead to large changes in overall demand.
- Health benefits are most likely to accrue in the smaller group of high use consumers; although a minority low use consumers may also gain some health benefits due to exploration of alternatives in therapy or medicines to codeine.
- Adverse health outcomes are still considered likely, even though average use is only 12.7 packs a year; there are consumers who are using substantially more packs per year and could develop dependence over time.

Five groups of consumers

The five different groups of consumers are set out in Figure 2 and are stratified according to type of use, type of pain and level of dependency.

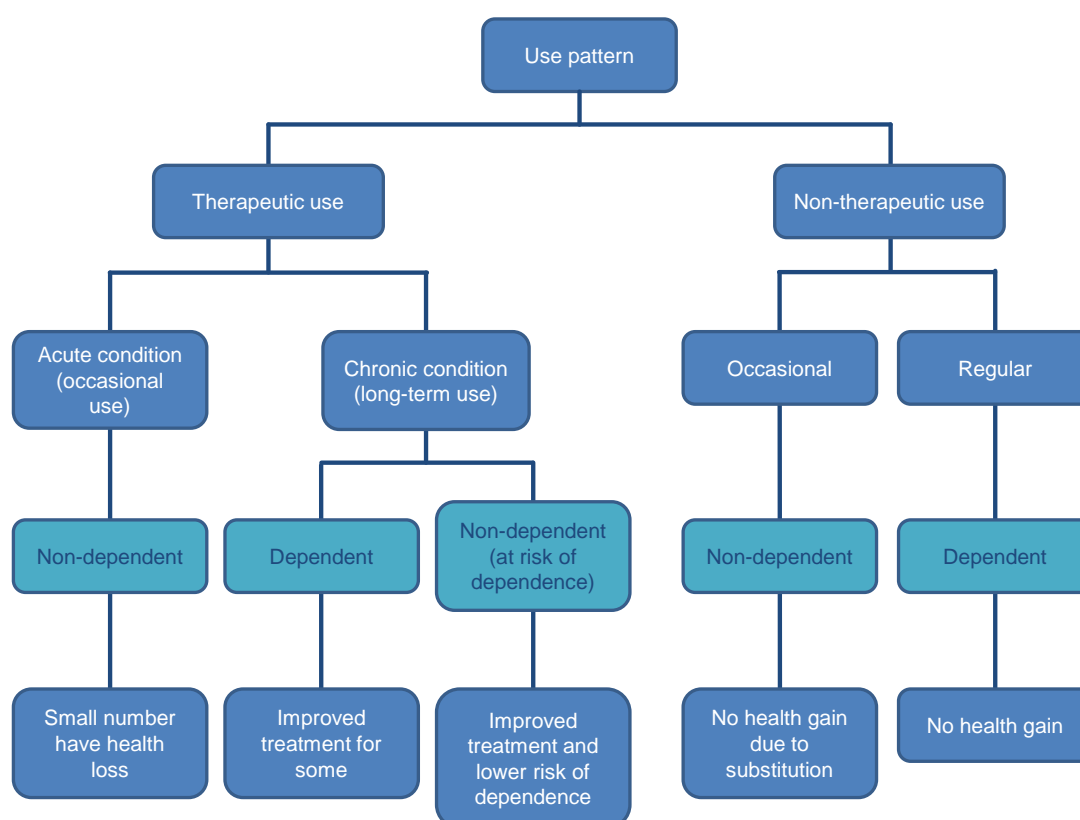


Figure 2: Patient/consumer groups used in the health economic modelling

(Source: KPMG Report: Figure E1)

Codeine use can be classified as either therapeutic or non-therapeutic. The classifications and the associated characteristics used in the economic model were derived from stakeholder consultations.

Therapeutic use can be stratified into chronic or acute use. Consumers that self-treat acute conditions are likely to non-dependent. These consumers might purchase only one or two packs per year and use it in a way consistent with the medical advice: i.e. for no more than 3 consecutive days without medical advice with no more than eight tablets a day.⁹¹ Consumers that suffer chronic pain conditions could be one of two types: non-dependent or dependent. Some chronic users are non-dependent and use only up to the maximum daily dose but use at this level for most days in a year. Frequent use can lead to dependence and indeed consumers that self-treat chronic pain with codeine are at greater risk of becoming dependent in comparison the consumers that self-treat acute pain conditions. In the economic model, dependent chronic consumers use more than the recommended maximum dose each day, whereas non-dependent consumers use the maximum recommended dose each day. Both types of chronic users use the low-dose codeine for the majority of days in a year, which in the base case is assumed to be 250 days> they are also more likely to consume the largest pack size (40 tablets) compared to acute users. Consequently, a regulatory change that restricts pack size to three days' supply will impact this group of consumers more so than acute users.

Chronic therapeutic use is more likely to result in adverse events such as gastrointestinal bleeds. They are also more likely to have an accidental death due to an overdose of codeine, although this is considered to be a very rare event.

While non-therapeutic use is often referred to in the media⁹², it is likely to be only a very small share of consumers in this group. Nonetheless, a conservative approach was used and this group was included in the total volume of sales. However, the model did not account for any benefits that might result from the proposed up-scheduling for this group. It is likely that use of low-dose codeine medicines will be limited substantially if they are required to go to a GP to obtain a script.

How many additional GP visits?

One approach to calculating the number of additional GP visits is to start with the estimated total current volume of packs sold and make an assumption regarding the rate at which consumers will go to a GP to obtain a prescription for this medicine, for example, on 40% of occasions. However this approach is based on an “*average consumer approach*” which, as discussed previously, can lead to a systematically biased estimate of the post-regulatory change if there are distinct types of consumers with different current use and different potential responses.

Some reasonable assumptions about the proposed regulatory changes that were made are:

- There will be additional GP consultations associated with ongoing utilisation of the current Schedule 3 codeine-containing medicines and these are considered separately from the additional consultations regarding different treatment pathways’.
- The GP will be able to provide up to five repeats (based on the level of repeats associated with current Schedule 4 codeine-containing medicine, and the option to use private scripts).

⁹¹ “Do not take more than a few days at a time unless your doctor tells you to.” Source: Mersyndol DayStrength Caplets Consumer Medicines Information “Developed by the pharmaceutical company responsible for this medicine in Australia, according to TGA regulations.”

<http://www.nps.org.au/medicines/pain-relief/combination-simple-pain-relievers/paracetamol-codeine/mersyndol-daystrength-caplets> Accessed August 24th

⁹² See, for example, “Codeine addiction a growing problem as Aussies abuse over-the-counter pain medication” Leisa Scott QWeekend The Courier-Mail August 31, 2013

<http://www.couriermail.com.au/news/queensland/codeine-addiction-a-growing-problem-as-aussies-abuse-overthecounter-pain-medication/story-fnihsrf2-1226707777107>

- Not all trips to the GP will be solely for the purpose of obtaining a prescription for codeine as some patients will request a script as part of a consultation that would otherwise have occurred.
- Different consumers will respond differently to the up-scheduling of codeine and to restrictions on the availability of codeine-containing medicines, depending upon whether they have acute or chronic pain.
- GPs will also respond to the actions of their patients. I.e. if their patients come every two weeks for an additional supply then they may refer them to a service such as a pain clinic.⁹³
- There is a limit to the number of additional consultations a consumer can have in a month, simply due to the financial and opportunity cost of attending a GP clinic.

By incorporating these reasonable assumptions in base case, the projected volume of additional GP visits in the base case is substantially lower than it would otherwise have been (refer to Annex 1, KPMG report, Table E3 for further information on the disaggregated approach to determine additional GP consultations.)

The number of additional GP visits is significantly lower than predicted by alternative models⁹⁴ due to two key differences; the use of a segregated population (see Figure 2) rather than an *average* consumer to predict additional consultations and the assumption that five repeats are available. The former brings a number of other factors into consideration, e.g., the additional constraints of the maximum additional visits any consumer could have in a week.

The Macquarie University Centre for the Health Economy (MUCHE) reported the results of a study on the value of OTC medicines.⁹⁵ The report stated that their survey found that, in the case of analgesics/pain relievers, when asked what they would do if the medicines for their condition became unavailable over the counter: 63% of respondents said they would see their doctor, 24% said they would do nothing, 15% said they would use a home remedy and 7% said they would 'supplement'. More options were explored in this economic model, due to the segregated population. If codeine was re-scheduled to schedule 4, 48% of all current users would use OTC paracetamol and/or ibuprofen medicines. Another 12% were assumed to visit their GP who would advise them to use OTC analgesics and/or non-pharmaceutical pain management options.

A report prepared for the Pharmacy Guild by Cadence⁹⁶ projected that there would be an additional 8.7 million GP visits as a consequence of up-scheduling low-dose codeine combination medicines at a cost of \$316.44 million as a result of patients attending a doctor for these scripts. The Cadence model assumes that 53% of all current users will continue if low-dose codeine medicines if they were up-scheduled and the additional GP costs correspond to one consultation per prescription. Targeted stakeholder consultations indicated that patients can have up to five repeat scripts (as is currently the case for prescription codeine products on private prescription), that is, a ratio of up to six scripts per GP visit, reducing the figure of \$316.44 million to as low as \$52 million.

⁹³ If a patient is referred to a pain clinic by their GP this attracts a rebate via the MBS (MBS items 2801 2806).

⁹⁴ Cadence Economics Pty Ltd, 'Fiscal Impact of Codeine Changes: Report for the Pharmacy Guild of Australia', dated 6 November 2015, viewed 24 August 2016, <<http://www.auspharmacist.net.au/images/cad.pdf>>.

⁹⁵ The Macquarie Centre for the Health Economy, Macquarie University, 'The value of OTC medicines in Australia: March 2014', <http://www.asmi.com.au/media/14036/final_web_copy_asmi_valuestudy_a4.pdf>. The report notes that 'it was funded by the Australian Self Medication Industry and a Macquarie University research grant'.

⁹⁶ Cadence Economics Pty Ltd, 'Fiscal Impact of Codeine Changes: Report for the Pharmacy Guild of Australia', dated 6 November 2015, viewed 24 August 2016, <<http://www.auspharmacist.net.au/images/cad.pdf>>.

Sensitivity analysis associated with GP visits

In the current economic model, the additional number of GP visits will vary between consumer subgroups (Figure 2), as different cohorts will consume different amounts of low-codeine medicines (Table 6).

Table 6: Type of current consumers and their pattern of use for Schedule 3 medicines only

	Number of consumers	Therapeutic use			Non-therapeutic use		
		Acute	Chronic dependent	Chronic not dependent	Chronic	Acute	Total
Total baseline use by type of consumer	As % of all users	80.0%	3.8%	15.2%	0.1%	0.9%	100%
	Number of packs	4,624,637	3,347,226	12,595,103	214,340	63,421	20,844,727
	As % of all packs sold	22.2%	16.1%	60.4%	1.0%	0.3%	100%
Total baseline expenditure	Total expenditure (\$M)	\$23.1	\$31.3	\$105.5	\$2.0	\$0.3	\$151.7

Of note:

- Around 6% of the Australian population over the age of 12 (19,874,413 at June 2015) purchase at least one pack of low-dose codeine per year. Given that there will be an estimated 20.8 million packs sold in 2017 and that many consumers purchase more than one pack, this result of 6% of the population purchasing at least one pack has face validity.
- 80 per cent of all consumers are 'acute' users; however, as a group they purchase 22.2% of all packs.
- 19% of all consumers are chronic therapeutic users and they purchase 76.5% of all packs sold.

For acute therapeutic users of low-dose codeine medicines (assumed to be 20% population and consume 5 packs/year), the up-scheduling of codeine will result in greater costs to the consumer and the government due to increased GP visits required for this group. However, increasing this population from 20% to 25% (acute therapeutic users with 50% increase in number of GP visits) results in approximately 0.3% increase in the net health benefit. That is, the model was insensitive to a change in the GP visits associated with acute users of low-dose codeine medicines.

Similarly, changing the percentage of consumers who use low-dose codeine medicines therapeutically, chronically and are dependent from 20% to 50%, and thus would require a GP visit to source codeine did not produce a significant change in the net health benefit (1% increase). Despite the higher treatment costs associated with chronic users that are dependent, due to the likely referrals to pain clinics, no significant change in net health benefit was noted when the percentage of users were changed. That is, the economic model was insensitive to the increase in number GP visits for this group.

Changing the percentage of consumers who use low-dose codeine medicines therapeutically, chronically but are non-dependent from 10% to 1%, reduced the net health benefit (-3.5%)

decrease). Even acknowledging that these patients are likely to visit the GP on a number of occasions, the economic model was relatively insensitive to the increase in number of GP visits for this group, despite this cohort consuming the greater number of medicine packs (Table 6).

The above sensitivity analysis indicates that additional GP visits associated with a up-scheduling of codeine does not significantly change the net benefits predicted from the economic model (that is GP visits is not a key input for this model). The key inputs were QALYs, the number of prescription repeats and the number of deaths prevented. Further sensitivity analysis is provide in the following pages of this RIS.

What are the health benefits?

The identified health benefits are of the following types (see KPMG report Annex E):

- prevention of accidental death;
- improved quality of life in the event that the patient is exposed to and benefits from, alternate pain treatment options that the patient would have not have otherwise used;
- For consumers taking combination therapy, potential for prevention of adverse events related to unintentional overdose of paracetamol or ibuprofen; and
- reduced dependence and risk of dependency.

If low-dose codeine is only available by prescription, then the health gains compared to the existing situation (low-dose codeine OTC) are driven by changes in treatment and therapy that result from changes in the availability of low-dose codeine OTC as an option. This change may arise as a result of the patient discussing alternative treatment options with their pharmacist or doctor (Figure 3). These alternative treatment options are available currently. The removal of the option of low-dose codeine OTC results in consumers exploring other options; it does not result in other options being introduced.

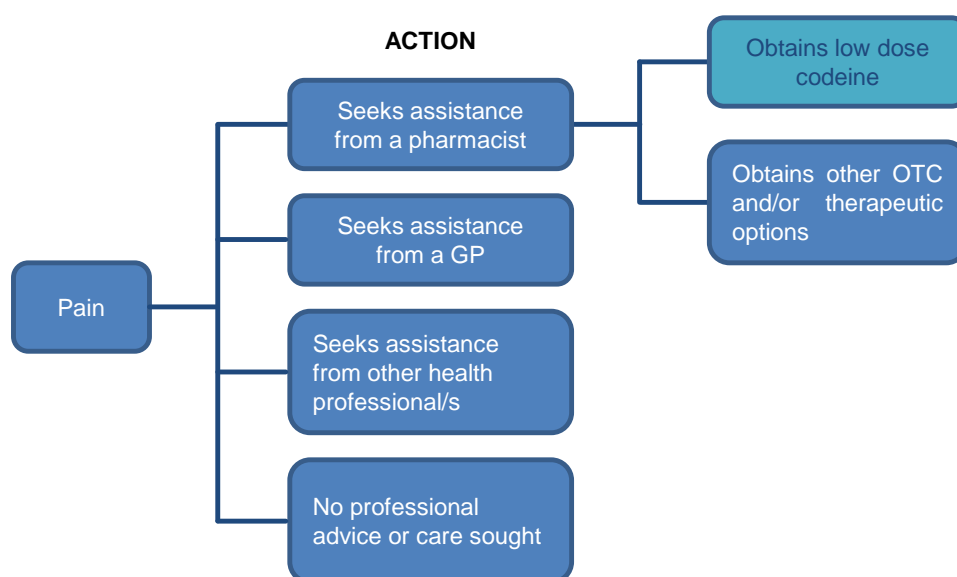


Figure 3: Potential patient actions and therapy options in response to pain

(Source: KPMG report Figure E2)

Consultation with a GP may result in the GP:

- assisting the patient in maintaining their current codeine usage by prescribing low/high dose codeine medicines;
- recommending the use of paracetamol or ibuprofen (or combinations) without codeine;

- recommending non-pharmacotherapy (such as exercise, physiotherapy etc.);
- prescribing alternative pharmacotherapy;
- referring the patient to allied health providers; and/or
- referring the patient to specialist pain clinics.

Furthermore, as a result of the patient visiting their GP, the cause of the patient's pain may be subsequently diagnosed and treated, ultimately reducing the patient's need for analgesics. When consumers are referred to allied healthcare professionals or specialist pain clinics by their GPs, then in many situations, patients will be able to obtain a Medicare rebate for the service. However, there are currently waiting lists for pain clinic services, so capacity constraints must also be considered.

Minor changes in consumer behaviour – is this a health benefit?

As discussed previously, when Schedule 2 codeine-containing analgesics were re-scheduled to Schedule 3 in 2010, no significant public health benefit was reported (*'Historical scheduling of codeine'* p. 31). While there are likely to be some minor changes in consumer purchasing behavior with reduction of pack sizes; these behaviors are unlikely to have any significant public health benefits (Refer to *'What are the health benefits?'* for further details on p. 55). Health benefits as shown in the model will only be realized from improved therapeutic pathways taken by patients who would otherwise be chronic therapeutic users of low-dose codeine.⁹⁷ For this improved therapeutic pathway to be realized the key enabler is a visit to a GP. However, this is unlikely to occur under options that retain OTC codeine-containing medicines, regardless of pack size or whether up-scheduled from Schedule 2 to Schedule 3.

The MedsASSIST program was not included in the modelling. However, the PGA has suggested that a combination in a reduction in pack size together with the use of mandated MedsASSIST program (which contains referral pathway modules that the program does not currently have [PGA, personal communication 2016]) could also lead to improved therapeutic pathways for consumers. While theoretically possible, there appear to be a number of operational limitations that are presented by this option. These limitations include:

- The increased instances of 'pharmacy shopping' to source codeine.⁹⁸ This is inconsistent with the limited ability of pharmacists to actively engage with *'challenging'* patients to manage the use of codeine in OTC medicines, noting that the pharmacy environment does not usually allow for private conversations in the way that doctors' rooms do (as outlined on p. 38 *'Real-time monitoring programs'*);
- States and Territories will need to agree to support MedsASSIST with mandatory reporting. Such changes require uniform adoption at the jurisdiction level and changes to relevant jurisdiction legislation, which would take time;
- Absence of a pharmacist-initiated patient referral system to pain management specialists or clinics for greater oversight and intervention (as is currently available for GPs);

⁹⁷ In the base case, only chronic therapeutic users of low-dose codeine have been included for the modelling of health benefits. It was raised in peak body consultations that some acute therapeutic users of low-dose codeine (e.g. migraine sufferers) may also benefit from improved therapeutic pathways; however, because this was assessed to be a low proportion of current acute users so this was not modelled in the base case.

⁹⁸ Fitzpatrick, L 2016 'Is codeine too easy to get in Australia? These young addicts think so' Vice. Posted online 5 May 2016. Accessed 25/11/2016: http://www.vice.com/en_au/read/pharmaceutical-opioid-addiction-in-australia.

- Pharmacist do not have the patients' full medical history, and thus are not best placed to advise on other therapeutic pathways that may be more beneficial, such as non-pharmacological or alternative pharmacological treatments;
- A recording and monitoring system is inconsistent in principle with scheduling of OTC medicines (Schedules 2 and Schedule 3);
- The voluntary MedsASSIST program, implemented by 65% of pharmacies, reports data that shows that approximately 2% of transactions have been denied, although about 6% sales have been made under duress in pharmacies (following a real or perceived threat to the safety of pharmacy staff);
- In the July and September reporting periods, approximately 20% of consumers purchased codeine products between 4 - 5 times and approximately 10% purchased products more than 5 times within a 7-month period; and
- In one particular example, an individual received 660 tablets over 3.5-month period despite their purchasing behaviour being tracked in MedsASSIST. This brings into doubt whether MedsASSIST is actually deterring access to codeine by consumers with codeine-dependence problems. The data does suggest that consumers with addiction problems will change their behaviour to source their codeine.

Noting the above issues, a key assumption in the model is that significant health benefits will be realized only from improved therapeutic pathways taken by patients after consultation with GPs as compared to continued chronic use of low-dose codeine products (see Figure 5, p. 83).⁹⁹ For further details refer to '*What are the health benefits?*' (p. 55). Other key assumptions and their base case values underpinning the economic analysis are:

- 99% of people who used low-dose codeine at least once are using it for therapeutic purposes with the remainder of consumers using it for non-therapeutic purposes.
 - Of all users, 80% are using it therapeutically for acute conditions
 - Of the 19% using it therapeutically for chronic conditions, 20% are dependent on low-dose codeine (i.e. of all users, 3.8% are dependent on low-dose codeine)
- For cough and cold products (currently Schedule 2): if up-scheduled to Schedule 4 then the prescribing behavior of GPs will be to provide zero repeats. As a liberal estimate, 20% of consumers are estimated to continue to use cough and cold products containing codeine and it is estimated that only 30% of these patients will make an additional visit to the GP to source these products compared to the GP visits they would have made anyway in the absence of the regulatory change.
- For Schedule 3 low-dose codeine-containing products: if up-scheduled to Schedule 4 then the prescribing behavior of GPs will be to provide up to 5 repeats (through authorized prescribing processes) if they assess that it is appropriate for this patient to continue with this pharmacotherapy, given the patient's symptoms and medical history.
- Projected number of prevented deaths from up-scheduling of codeine to Schedule 4 is 5 per year.

⁹⁹ In the base case, only chronic therapeutic users of low-dose codeine have been included for the modelling of health benefits. It was raised in peak body consultations that some acute therapeutic users of low-dose codeine (e.g. migraine sufferers) may also benefit from improved therapeutic pathways; however, because this was assessed to be a low proportion of current acute users so this was not modelled in the base case.

- Pharmaceutical companies are unlikely to seek PBAC approval for PBS listing of low-dose codeine; however, consumers are currently using low-dose codeine without a PBS subsidy and its price is currently below the general beneficiary co-payment. Prescribers of low-dose codeine can use a 'private script' (i.e. non PBS) with up to 5 repeats compared to PBS option with zero repeats. Therefore, it is unlikely that concessional consumers will choose a low-dose codeine PBS option with zero repeats, in order to access the PBS subsidy should one be available (which in itself is unlikely, noting a 30 mg codeine medicine is currently available through PBS). There is no financial advantage (no PBS subsidy) for a general beneficiary (non-concessional).
- Substitute low-dose codeine analgesics with paracetamol and/or ibuprofen products, that are cheaper than existing codeine products and readily available at supermarkets (which introduce further price competition).¹⁰⁰

What are the health costs?

For consumers and the Government the main additional costs relate to:

- net out-of-pocket costs to consumer (extra time spent to visit doctor);
- additional costs to MBS due to additional GP (exploration of alternative treatment pathways or to obtain access to low-dose codeine medicines) and referral to pain management clinics; and
- additional costs to the PBS due to additional scripts for PBS listed pain medications (alternatives to low-dose codeine medicines).

The additional costs to the MBS are the primary driver of additional costs to government (refer to Table ES8 of KPMG report).

Key modelling parameters – current use pattern

Four steps are taken to determine the key modelling parameters given available data (sales data from IMS), reasonable assumptions about the number of tablets consumed per day, days of use for each of the five types of consumers, and the share of total consumers in each group (Figure 4). These four steps are outlined below, with the inputs to steps 1, 2 and 3 having been informed by discussions with stakeholders:

- The total number of sales by pack size (dollar value and packs sold) was calculated from the IMS data. The total retail sales value by pack size was calculated by assuming a 44 per cent retail mark up.¹⁰¹
- 6-20 tablets per day over 12-365 days per year depending on the type of consumer.

¹⁰⁰ This price is based on the following results of a Choice survey in July 2015. 'Supermarket generic paracetamol was a lot cheaper than Panadol, costing from 65c (Aldi) to 70c (Coles and Woolworths) for a pack of 20. In pharmacies, however, a pack of 100 Panamax can be had for less than \$2, making this one of the cheapest painkillers you can buy. Nurofen (ibuprofen) was generally cheaper in pharmacies than supermarkets, with the bigger packs making it even more so. However, supermarkets were the cheapest source of generic ibuprofen, at \$1.65 (Aldi) to \$1.80 (Coles) per pack of 24. In Chemist Warehouse we found 50 Rafen tablets for \$2.39, but in other pharmacies, house brands such as Amcal and Chemists Own were more expensive than supermarket generics.' <<https://www.choice.com.au/health-and-body/medicines-and-supplements/prescription-medicines/articles/supermarkets-vs-pharmacies-for-otc-medicine>>.

¹⁰¹ The total sales values and units by pack size were used to estimate the wholesale prices of both IMS Schedule 2 and Schedule 3 codeine-based medicines. The retail prices of those codeine-based medicines were captured from the retail market in Australia. The retail mark-up is then estimated by employing both wholesale and retail values of codeine-based medicines

- a) Therapeutic, acute pain, non-dependent – 8 tablets/day over 12 days/year
 - b) Therapeutic, chronic pain, non-dependent – 8 tablets/day over 250 days/year
 - c) Therapeutic, chronic pain, dependent – 12 tablets/day over 250 days/year
 - d) Non-therapeutic, occasional use, non-dependent – 6 tablets/day over 20 days/year
 - e) Non-therapeutic, regular use, dependent – 20 tablets/day over 365 days/year
3. The proportion of consumers in each group
- a) Therapeutic – 99%, of whom:
 - a. Therapeutic, acute pain, non-dependent – 80% of all users
 - b. Therapeutic, chronic pain – 19%% of all users of whom:
 - 1. 40% are therapeutic, chronic pain, non-dependent
 - 2. 60% are therapeutic, chronic pain, dependent
 - b) Non-therapeutic – 1%, of whom:
 - a. 10% are non-therapeutic, regular use, dependent
 - b. 90% are non-therapeutic, occasional use, non-dependent
4. The pack sales were then allocated by the model across consumers, starting with the smaller packs allocated to the lower use consumers (20 tablets), and with the maximum pack sizes (40 tablets) allocated last to the most frequent users.

This approach enabled the average pack size and expenditure per consumer group to be calculated. In turn, this allowed the assessment of the plausibility of changes to current behaviour based on a more accurate picture of the current pattern of use.

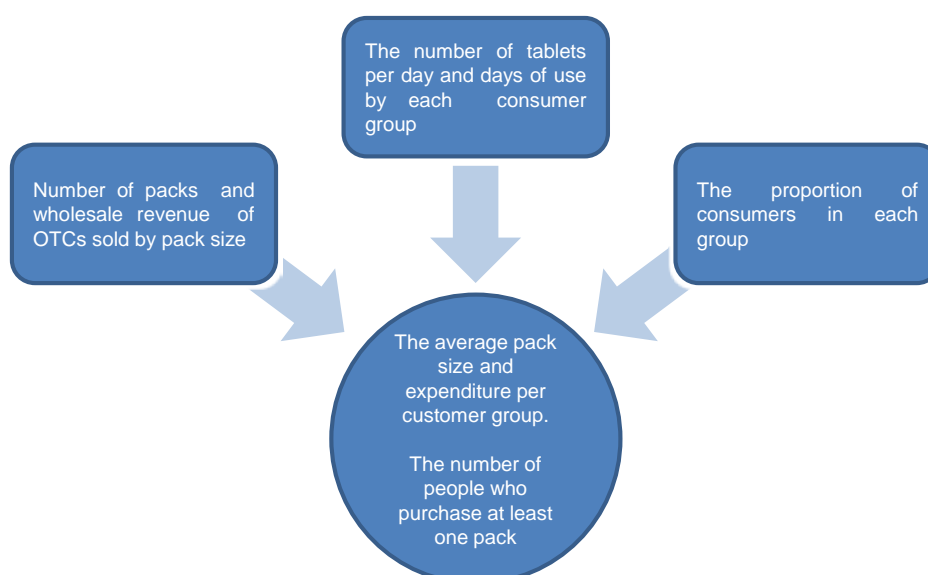


Figure 4: Determining key modelling parameters

Sensitivity analyses

Sensitivity analyses were performed to test the robustness of the key summary statistic, the net benefit, to the model's inputs (refer to Annex 1, KPMG Report Table E4 for further details).

The sensitivity analysis indicated that a positive net benefit is maintained under all plausible assumptions regarding the possible values of the model's inputs. The net benefit remained positive even when the following (highly unlikely) values for inputs were assumed:

- Reducing the benefit
 - No deaths are prevented (compared to 5 per year)
 - The average QALY benefit per treated patient decreases by 80%
- Increasing the costs
 - There are no repeats for low-dose codeine (increases the number of GP consultations)
 - The cost per patient who is treated increases by 80 %

Therefore, it can be concluded that the model's key statistic, the net benefit, is very likely to be positive.

Results

The overall results for regulatory costs, economic costs and benefits are presented in Table 20 (refer to *'Net benefit for each scenario'* p. 85). The main result is the net benefit, which is presented using two subset results for the first year and tenth year net benefit. These yearly results are further subdivided into: (1) first year benefit, cost and net benefit; and (2) the ten year NPV benefit, cost and net benefit. Option 6 is the only option with a net benefit hence all other options have a net economic cost, driven by additional out-of-pocket costs to consumers as well as the cost attributed to the administrative burden for businesses and individuals.

In many scenarios there was a net reduction in out of pocket costs to the consumer. When this occurs, the model adjusts the resultant saving to be included as a benefit, not a negative cost. This saving to consumers is the result of a combination of factors, including:

- the reduction in use of low-dose codeine
- the substitution of low-dose codeine with cheaper supermarket products such as paracetamol or ibuprofen
- patients who continue with prescription medicines (whether containing codeine or not) in most cases will pay the same or less than their current expenditure on low-dose OTC codeine medicines
- if patients substitute low-dose codeine medicine with high dose prescription codeine medicine via script, they can be provided with up to five repeats by their GP, thus reducing the need for visits to their GP
- the high bulk-billing rate for GP consultations
- the rate at which pain-related GP consultations can be accommodated within visits that would otherwise have occurred in the absence of the proposed regulatory change.

One potential issue raised by the modelling is that the predicted demand for additional consultations at pain clinics is unlikely to be accommodated within existing capacity.

Most stakeholders indicated that additional face-to-face education¹⁰² for prescribers and pharmacists was unlikely to be necessary. With an estimated one million people using at least one Schedule 3 low-dose codeine product a year, the need to invest in an education and awareness campaign, particularly for consumers, is apparent. This issue was raised with stakeholders. The question of how an education campaign for consumers would be funded, and what form it might take, is still to be determined and is dependent on the regulatory process changes, if any. The cost of this campaign was not included in these estimates.

Individual options

Option 1: Status quo

Option 1 represents the *status quo*, that no changes to the scheduling of medicines containing codeine are made.

Codeine, under the status quo, will remain available 'over-the-counter' in low-dose preparations as cough and cold medicines (10* mg or less) and in combination analgesics with other pain relief medicines (12* mg or less) in pharmacies. High dose codeine preparations (greater than 30* mg) will continue to be available by prescription only.

Under this option there will be no change to the current scheduling of codeine, no change in pack size would be required, and the inclusion of an additional advisory warning statement on labels that '*codeine can cause addiction*' would remain voluntary. The inconsistencies relating to the current scheduling of codeine (see '*Current scheduling inconsistencies*' p. 35 and Table 7, below) would remain.

¹⁰² Also known as 'Academic detailing', this is the process of delivering face-to-face education of prescribers by trained healthcare professionals, typically pharmacists, physicians, or nurses. The goal of academic detailing is to improve prescribing of targeted drugs to be consistent with medical evidence from randomized controlled trials, which ultimately improves patient care and can reduce health care costs.

* The concentration of the codeine ingredient on the medicine pack may be different due to the salt component.

Table 7: Requirements for codeine in the current Poisons Standard

	Dosage unit	Maximum daily dose	Pack Size	Type
Schedule 2 (Pharmacy medicine)	10 mg or less ¹⁰³	60mg	6 days	Cough and cold
Schedule 3 (Pharmacist Only medicine)	12 mg or less	100mg	5 days	Analgesics
Schedule 4 (Prescription only medicine)	30 mg or less	Not prescribed	Not prescribed	

Source: KPMG 2016, Table D2

Under the current scheduling status of codeine (Schedule 2 and Schedule 3), low-dose codeine preparations will be available in the pharmacy. Access to Schedule 3 low-dose codeine preparations is available after the consumer obtains adequate advice from a pharmacist (or licenced person).¹⁰⁴ However, industry consultation has suggested that this consultation process may be limited operationally by a lack of private consultation areas in most pharmacies,¹⁰⁵ subsequently resulting in consumers being inadequately informed of the risks of low-dose codeine preparations compared to alternatives (both pharmacological and non-pharmacological), and/or the inappropriateness of low-dose codeine medicines being used long-term.

Under the status quo, it is likely that the significant public health issues such as codeine-related deaths (with and without other drug toxicity) associated with the misuse of codeine, and attributed to its wide accessibility,³⁸ will continue to rise by at least 9.3% each year.¹⁰ For further details refer to 'Morbidity and death' (p. 20) and 'Health costs and benefits' for Option 1 (below).

Impacts

As Option 1 represents the status quo, there are no anticipated impacts on the medicine industry (such as direct compliance costs), consumers or healthcare professionals.

Regulatory costs

There are no direct costs associated with this option as the status quo has been used as a baseline with which to compare the regulatory costs associated with the implementation of the other options.

Health costs and benefits

Whilst Option 1 represents the *business as usual* scenario and therefore has no direct regulatory impact, this option does not address the range of concerns that has been identified with the current scheduling of codeine, such as lack of education and significant evidence of harm.

¹⁰³ References to the dosage unit of codeine in the Poisons Standard refer to anhydrous codeine. This can be multiplied by 1.33 to convert to codeine phosphate. This is important to note because dosages set out in ARTG entries refer to concentrations of codeine phosphate, whereas dosages in the Poisons Standard refer to anhydrous codeine.

* The concentration of the codeine ingredient on the medicine pack may be different due to the salt component.

¹⁰⁴ Poisons Standard November 2016. Available at: <https://www.legislation.gov.au/Details/F2016L01638>

¹⁰⁵ TGA consultation with industry groups.

There are no net health benefits associated with Option 1; however the cost to the healthcare system over time will increase as health outcomes related to codeine misuse and abuse deteriorate. Furthermore, given the lack of efficacy in certain individuals, risk of dependency to codeine-containing medicines that can lead to an increase in the level of abuse or misuse, and safety concerns associated with rapid metabolisers of codeine, there is a significant net health burden that should not be dismissed.

Notwithstanding the re-scheduling of OTC codeine products from Schedule 2 to Schedule 3 in 2010, there have been numerous reports of adverse outcomes and codeine dependence suggesting that this re-scheduling has not been effective (see p 32 '*How effective were the scheduling changes for codeine in 2010?*' and references therein).

While codeine-containing analgesics remain available OTC, it is less likely that patients using codeine for chronic pain will seek advice from GPs. Hence alternative treatment pathways and other treatment options, including referral to a pain management clinic, non-pharmacological interventions, or alternative pharmaceuticals, are less likely to be explored. Further, without changes to reduce the pack size to not more than 3 days' supply and include a label warning that '*codeine can cause addiction*', no change in patient behaviour is likely for codeine-dependent individuals.

On this basis, for Option 1 (no change) it is anticipated that individual health outcomes would continue to deteriorate for consumers who abuse or misuse codeine. This option will not drive positive changes in consumer use behaviour, will not raise awareness of codeine dependency and will not encourage exploration of alternative treatment pathways.

As there is no catalyst for change under this option, the public will continue to access and self-treat their conditions with codeine-containing medicines that are presumed to have no adverse health risks due to the relatively limited access restrictions. However, the most concern under this option is that the current identified public health issues of morbidity and deaths will remain.

Option 2: Reduce pack size of Schedule 2 and new label warning

Under Option 2 the current Schedule 2 entry for codeine in cough and cold medicine preparations would be amended to reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction. The changes and regulatory impacts are summarised in Table 8.

Table 8: Regulatory impacts of Option 2

	Current	Proposed change	Impact
Distribution model	Schedule 2	Schedule 2	Nil
Label	Advisory statement for addiction not required	New advisory statement	Update label
Pack Size	6 days' supply	3 days' supply	Reduce pack size
Dosage	10 mg per dosage unit 60 mg per day	No formulation change	Nil
ARTG, CMI and PI	Registered	Update ARTG entry	Updated ARTG entry

Source: KPMG 2016, Table D5

This option will affect 46¹⁰⁶ ARTG medicine entries (entirely OTC) across 15 sponsors (Table 4, p. 45). The same baseline assumption has been used as outlined under Option 1.

As explained above, historically, changing the labelling and decreasing the pack size has not adequately addressed the problem of misuse, dependence or medicine misadventure. Of note, however, is that MHRA has incorporated these changes into a multi-faceted approach to the regulation of codeine-containing medicines and have noted a reduction in sales of these products since the changes were introduced in 2009. The significance of the reduction in sales of these medicines in addressing the public health issues is unclear.

MHRA have also limited indications for non-prescription use to short-term treatment of acute pain which is not relieved by paracetamol, ibuprofen or aspirin alone. Further risk minimisation measures included the strengthening of the warnings in PI, CMI, labels and advertising, and educating consumers about the importance of not taking medicines for more than 3 days consecutively and the need to seek advice from a doctor if required for more than 3 days.

Regulatory cost assumptions for Option 2

- Several sponsors have recently implemented advisory warnings against codeine addiction as part of industry initiatives; however some additional labelling changes would likely be required as a result of the reduced pack size. Based on the baseline assumptions, 115 OTC medicines¹⁰⁷ currently marketed in Australia will be affected (Table 4, p. 45).
- As noted in the business-as-usual (BAU) costs, it is estimated that half of the product label updates can be rolled into already planned updates reducing the per product cost by 50% for that segment. Therefore the carry-forward figure is that 58 labels will need to be updated in addition to BAU labelling activities.
- Based on BAU costs outlined in Option 1, the label pre-production and production costs are estimated to be \$0.24 million.
- Consultations have identified that approximately 50% of codeine sponsors already produce 3-day packs or have a production line that could accommodate this change across their impacted product portfolio, provided the implementation timeframe is sufficient. These sponsors will not need to implement new manufacturing arrangements for either the outer carton (apart from the printing) or inner blister pack. It is estimated that approximately 8 sponsors will incur costs to change their pack size.
- For the impacted sponsors, it is estimated from industry consultations that the up-front cost to implement the required packaging changes is \$30,000 per sponsor. This could include re-tooling to modify blister pack lengths or reduce packaging depth. It should be noted that these costs can vary depending on the location of the manufacturing facility being used. For example, changes can be implemented more quickly in domestic facilities but are more expensive, whereas changes in overseas facilities can be implemented at lower cost, but are subject to longer delays due to competing priorities.
- The required changes fall under a C1 application level¹⁰⁸ based on a review of the applicable forms, and consultation with sponsors, it is estimated that 4 hours will be required to prepare and submit the relevant form. The cost of completing the required form is estimated to be \$0.012 million.

¹⁰⁶ KPMG has assessed that there will be no rationalisation of ARTG entries if this option is implemented, so all existing entries (46) need to be updated on the ARTG.

¹⁰⁷ Number of existing Schedule 2 entries x multiplier to account for ARTG entries covering for more than one medicine unit.

¹⁰⁸ For more information regarding change applications, see the TGA website at <https://www.tga.gov.au/book-page/step-2-determining-your-application-level-and-change-codes>

- Note that the estimated regulatory compliance costs do not account for the application fees that sponsors would have to pay (roughly \$1,500 per listing update) as direct financial costs are outside the scope of the Regulatory Burden Measurement (RBM) framework.¹⁰⁹ Similar exclusions also apply to the other 4 options.

Impacts

Impact on the medicines industry

Current sponsors of Schedule 2 products with codeine-containing medicines would be required to update their labels to reflect the reduced pack size as well as include a new advisory statement that codeine can cause addiction (less those that already contain this advisory statement – currently voluntary). Current sponsors who do not already have a 3-day pack in their production portfolio would need to implement new manufacturing arrangements. All sponsors would need to complete the required documentation to effect the required change to their ARTG entries.

Impact on consumers and healthcare professionals

There are no predicted impacts on healthcare professionals.

Due to the reduction in pack size, consumers are expected to spend more to maintain current codeine use, including the use of codeine-containing cough and cold medicines, despite it being contraindicated for use in children under 6 years of age¹¹⁰ and evidence to suggest that codeine has limited efficacy for symptomatic relief of cough compared to placebo.^{111, 112, 113, 114, 115}

As there are no expected changes in treatment or therapy for those consumers currently abusing low-dose codeine medicines, there are no predicted health gains under Option 2 for this subset of the population.

Due to the label changes and the reduction pack sizes, there may be a small increase in awareness of risks associated with the use of codeine-containing medicines. However, as pharmacist consultations are not required for Schedule 2 medicines, this increased awareness is likely to be minimal and limited to those consumers who read the label warning statements. The small health benefit is unlikely to be sustainable if a subset of these consumers go on to develop dependence to codeine.

Interestingly in a study that reviewed the gaps in consumers knowledge of cough and cold medicines¹¹⁶, the main concerns for consumers were related to the potential for medicine

¹⁰⁹ OBPR, Regulatory Burden Measurement (RBM) guidance note, <https://www.dpmc.gov.au/sites/default/files/publications/005-Regulatory-Burden-Measurement-Framework.pdf>, February 2016

¹¹⁰ NPS Medicinewise, Cough and cold medicines. Published online on 23 August 2012. Accessed on 28 November 2016: <http://www.nps.org.au/medicines/respiratory-system/cough-and-cold-medicines>

¹¹¹ Bolser, D.C. (2006) 'The Cough Suppressant and Pharmacologic Protussive Therapy : ACCP Evidence-Based Clinical Practice Guidelines', *Chest Journal*, 129 (1 suppl), 238S-249S.

¹¹² Eccles R, *et al.* (1992) 'Lack of effect of codeine in the treatment of cough associated with acute upper respiratory tract infection', *Journal of Clinical Pharmacy and Therapeutics*, 17(3), pp. 175-80.

¹¹³ Freestone C *et al.* (1997) 'Assessment of the antitussive efficacy of codeine in cough associated with common cold', *Journal of Pharmacy and Pharmacology*, 49, pp. 1045-9.

¹¹⁴ Pavesi L, Subburaj S, Porter-Shaw K (2001) 'Application and validation of a computerized cough acquisition system for objective monitoring of acute cough: a meta-analysis; *Chest*, 120, pp. 1121-1128.

¹¹⁵ Bolser, D.C and Davenport, P.W (2007) 'Codeine and cough: an ineffective gold standard', *Curr Opin Allergy Clin Immunol*, 7 (1), pp. 32-36.

¹¹⁶ <http://www.racgp.org.au/afp/2015/july/self-medication-for-cough-and-%E2%80%A8the-common-cold-information-%E2%80%A8needs-of-consumers/> accessed November 2016

interaction, side effects and delay in diagnosis. Consumers appeared to be poorly informed of the appropriate use, efficacy and safety of OTC medicines for respiratory symptoms despite the risks.¹¹⁷ Most consumers believe that cough and cold medicines can cure or shorten the duration of an illness, rather than simply provide symptomatic relief. On this basis, greater awareness of the risks posed by codeine-containing cough and cold medicines may also encourage conversations about the use of such medicines in relieving symptoms.

The regulatory cost calculations (RBM) for Option 2 is reported in Table D7 of the KPMG Report (2016) in Annex 1 (and is provided below).

Impact on the government

No impact on government operations are expected from the implementation of Option 2.

Regulatory costs

The average annual regulatory costs (Table 9) for Option 2 when averaged over 10 years are estimated to be \$0.05 million. This net regulatory cost accounts for BAU relabelling that occurs frequently. The total regulatory costs over 10 years (2017-2026) are \$0.5 million.

Table 9: Average annual regulatory costs (from business as usual) for Option 2

Change in costs (\$million)	Business	Community organisations	Individuals	Total change in costs
Total, by sector^{a, b}	0.05	0.00	0.00	0.05

^a From business as usual; ^b Change in costs (\$millions); Source: KPMG 2016, Table D7

Health costs

The health economic costs for the period 2017-2026 for Option 2 are estimated to be \$20.70 million; these costs are principally driven by the increase costs to consumers.

Health benefits

Under Option 2 the current Schedule 2 entries for codeine in cough and cold medicine preparations would be amended to reduce the pack size to not more than 3 days' supply and include a label warning that '*codeine can cause addiction*'.

As detailed in the economic model, very limited health benefits are likely to be realized by the implementation of Option 2, and these would be principally driven by minor changes in consumer buying behaviour due to the label changes and the reduced pack sizes. Consumers would need to visit the pharmacy more often to source these medicines due to smaller pack size. It is unclear whether visiting the pharmacy more often will result in an increased awareness of the risks of codeine. The label warning statement is more likely to raise awareness of risks associated with codeine, leading to some health benefits for a small subset of the population that consume these products, especially for those consumers that may be unaware that their usual brand of cough and cold product contains low-dose codeine, and the inclusion of this may not have any substantial therapeutic benefit. No benefits are likely to be associated with consumers that are dependent on codeine.

¹¹⁷ Johnson G and Helman C (2004) Remedy or cure? Lay beliefs about over the counter medicines for coughs and colds, *Br J Gen Pract*, 54(499):98-102

From the health economic model, significant health benefits only arose when improved therapeutic pathways were taken by patients who are chronic users of low-dose codeine. For this improved therapeutic pathway to be realized the key enabler was a visit to a GP, which will not occur under this option.¹¹⁸ Option 2 is likely to occur simultaneously with Option 5 (reduce the pack size for Schedule 3 medicines to not more than 3 days' supply and include a label warning that '*codeine can cause addiction*') such that consistency in the packaging and labelling of all OTC codeine-containing medicines is achieved. This is discussed under Scenario 3.

Schedule 2 codeine-containing medicines represent the smallest subset of these medicines on the market, and thus reducing the pack size to not more than 3 days' supply is unlikely to have a substantial effect on health benefits for individuals or the broader community. Implementation of Option 2 is likely to have an impact similar to Option 1, which is the status quo. It is anticipated that individual health outcomes would continue to deteriorate for consumers who abuse or misuse codeine, and the resulting costs to the healthcare system over time will increase.

Option 3: Up-schedule Schedule 2 to 3, reduce pack size and new label warning

Under Option 3 the current Schedule 2 entries for codeine would be up-scheduled to Schedule 3, and the pack size would be reduced to not more than 3 days' supply and include a label warning that codeine can cause addiction. The changes and regulatory impacts are summarised in Table 10.

Table 10: Regulatory impacts of Option 3

	Current	Proposed change	Impact
Distribution model	Schedule 2	Schedule 3	Consumer must now speak with pharmacist
Label	Advisory statement for addiction not required	New advisory statement	Update label
Pack Size	6 days' supply (Schedule 2)	3 days' supply	Reduce pack size
Dosage	10 mg per dosage unit, 60 mg per day	No formulation change ^a	Nil
ARTG, CMI and PI	Registered	Update ARTG entry	Updated ARTG entry including new CMI and PI

^a The implementation of Option 3 would result in the creation of two classes of codeine products within Schedule 3: 10 mg/dose, 60 mg/day and 12 mg/dose, 100 mg/day; Source: KPMG 2016, Table D8.

¹¹⁸ No data was able to be sourced by the Consultant that would enable the modelling of health benefits arising from smaller pack sizes or additional advisory warnings. While such changes might, conceivably, have some impact on the low-dose codeine use by acute therapeutic users, this population is not responsible for the rising health costs from codeine abuse/misuse. In relation to the chronic therapeutic population, particularly the dependent sub-group, which likely accounts for the majority of the health costs from low-dose codeine abuse/misuse, in the absence of specific data to the contrary, it is assessed that they will modify their buying habits to maintain their codeine use, thereby negating any projected health benefits.

This option will affect 46¹¹⁹ ARTG medicine entries (entirely OTC) across 15 sponsors (Table 4, p. 45). The same baseline assumption has been used as outlined under Option 1.

Regulatory cost assumptions for Option 3

- Several sponsors have recently implemented advisory warnings for codeine addiction as part of industry initiatives; however, some additional labelling changes would likely be required as a result of the reduced pack size. Based on the baseline assumptions, 115 OTC medicine products currently marketed in Australia will be affected (Table 4, p. 45).
- It is estimated that all Schedule 2 sponsors will migrate their products to Schedule 3, but with a rationalisation of their product portfolio by 50% to reflect the reduced range that would be expected as products move behind the pharmacy counter, which faces stronger competition for space. Therefore the carry-forward total into the model is 58 products. As noted in the BAU costs it is estimated that half of the product label updates can be rolled into already planned updates reducing the per product cost by 50% for that segment; therefore the carry forward figure is 29 labels that will need to be updated in addition to BAU labelling activities.
- Based on BAU costs outlined in Option 1, the label pre-production and production costs are estimated to be \$0.33 million.
- Consultations have identified that roughly 50% of codeine sponsors already produce 3-day packs or have a production line that could accommodate this change across their impacted product portfolio, provided the implementation timeframe is sufficient. These sponsors will not need to implement new manufacturing arrangements for either the outer carton (apart from the printing) or inner blister pack. It is estimated that approximately 8 sponsors will incur costs to change their pack size.
- For the impacted sponsors, it is estimated from industry consultations that the up-front cost to implement the required packaging changes is \$30,000 per sponsor. This could include re-tooling to modify blister pack lengths or reduce packaging depth. It should be noted that these costs can vary depending on the location of the manufacturing facility being used. For example, changes can be implemented more quickly in domestic facilities but are more expensive, whereas changes in overseas facilities can be implemented at lower cost, but are subject to longer delays due to competing priorities.
- Based on BAU costs outlined in Option 1, and the factors listed above, packaging transition costs are estimated to be \$0.24 million.
- The required changes fall under a C2 application level,¹²⁰ based on a review of the applicable forms, and consultation with sponsors, it is estimated that 12 hours will be required to prepare and submit the relevant forms (including the creation of PI and CMI documentation). This estimate assumes that current Schedule 2 sponsors will adopt the efficient practice of replicating the PI documentation of a generic product already in the market. It is also possible that a core PI would be available from similar medicines already available and this would assist industry with an efficient migration of these products, which would further reduce costs. The cost of completing the required form and provision of supporting materials is estimated to be \$0.036 million.

¹¹⁹ The number of ARTG entries under Option 3 is the same as under Option 2. Although some product portfolio rationalisation is likely to occur (50% of products) there are, generally, multiple medicine units (e.g. different pack sizes) per ARTG entry (a planning figure of 2.5 medicines per ARTG entry for OTC medicines has been used). On this basis, KPMG has assumed that no current sponsors will allow existing ARTG listings to lapse if this option is implemented.

¹²⁰ For more information regarding change applications, see the TGA website at <https://www.tga.gov.au/book-page/step-2-determining-your-application-level-and-change-codes>

- The re-scheduling of Schedule 2 medicines to Schedule 3 would require individuals to speak with a pharmacist prior to making a purchase of codeine-based cough and cold products. In the absence of data it has been estimated this will consume an additional 30 seconds of time for both the individual and the pharmacist.
- Current sales data indicates roughly 4.4 million packets of codeine-based Schedule 2 cough and cold products are sold every year in Australia. In the absence of data to forecast the market responses to Option 3, it is estimated that aggregate demand for Schedule 2 products would drop by 25% if re-scheduled to Schedule 3. It is therefore estimated that there will be an additional 3.3 million Schedule 3 transactions/conversations per year in response to the Schedule 2 to Schedule 3 re-scheduling.
- The regulatory cost calculations (RBM) for Option 3 is reported in Table D9 of the KPMG Report (2016) in Annex 1, with overall regulatory costs presented below in Table 11.

Impacts

Impact on the medicines industry

Current sponsors of Schedule 2 products with codeine as an active ingredient would be required to update their labels to reflect the change from Schedule 2 to Schedule 3 and the reduced pack size, in addition to including a new advisory statement that codeine can cause addiction (less those that already contain this advisory statement – currently voluntary). Current sponsors who do not already have a 3-day pack in their production portfolio would need to implement new manufacturing arrangements. All sponsors would need to complete the required documentation to effect the required change to their ARTG entries.

Impact on consumers and healthcare professionals

The change from Schedule 2 to Schedule 3 would require customers to speak to a pharmacist prior to making a purchase of codeine-containing cough and cold products. Due to the reduction in pack size, consumers are expected to spend more to maintain current codeine use. For the individual who is dependent on codeine and consumes Schedule 2 products, there may be localised health benefits for the individual (from speaking with a pharmacist). At a higher level however, only very minimal gains in health outcomes are expected for those consumers currently abusing low-dose codeine as there will be only minimal changes in treatment for these consumers. (For further details see p. 52 '*How many additional GP visits?*'). This conclusion is consistent with the outcomes of the 2011 re-scheduling of codeine from Schedule 2 to Schedule 3, which did not achieve the required reduction in harm to affected individuals. Although inclusion in Schedule 3 may have initially decreased abuse of codeine-containing products, the number of patients presenting for codeine detoxification have continued to grow since 2010.

Impact on the government

No impact on government operations are expected from the implementation of Option 3.

Regulatory costs

The average annual regulatory costs (Table 11) for Option 3 are estimated to be \$10.14 million when averaged over ten years. Total regulatory costs for 2017-2016 are \$101.40 million. This net regulatory cost accounts for BAU relabelling that occurs frequently.

Table 11: Average annual regulatory costs (from business as usual) for Option 3

Change in costs (\$million)	Business	Community organisations	Individuals	Total change in costs
Total, by sector^{a, b}	6.95	0.00	3.19	10.14

^a From business as usual; ^b Change in costs (\$millions); Source: KPMG (2016) Table D10

Health costs

The health economic costs for Option 3 are estimated to be \$14.49 million for the period 2017-2026 (7% discounted); these costs are principally driven by the increased costs to consumers.

Health benefits

Under Option 3 the current Schedule 2 *Pharmacy Only* entries for codeine in cough and cold medicine preparations would be up-scheduled to Schedule 3 *Pharmacist Only*, and the pack size would be reduced to not more than 3 days' supply and include a label warning that '*codeine can cause addiction*'.

The label changes and the reduced pack size is likely to result in an increased number of pharmacy consultations at the time of dispensing, and therefore a small increase in awareness of risks associated with codeine is likely. This will be limited to those consumers that experience adequate consultations with pharmacists, or who read the product label. The small health benefit is unlikely to be sustainable if a subset of these consumers goes on to develop dependence to codeine, due to the subsequent public health issues.

As detailed in the economic model, no significant health benefits will be realized by the implementation of Option 3. As described earlier in the report, the only projected significant health benefits arose from improved therapeutic pathways taken by patients who are chronic users of low-dose codeine. For an improved therapeutic pathway to be realized the key enabler was a visit to a GP, which would unlikely occur under this option. Option 3 (up-schedule Schedule 2 to 3) is likely to occur simultaneously with Option 5 (reduce the Schedule 3 pack size to not more than 3 days' supply and include a label warning that '*codeine can cause addiction*'). This combination is discussed under Scenario 3.

Schedule 2 codeine-containing medicines represent the smallest subset of OTC codeine-containing medicines on the market. Making these medicines *Pharmacist Only*, reducing the pack size (3 days' supply) and including a label warning is likely to have a small effect on health benefits for the consumer. For this option, the requirement to consult with a pharmacist to purchase codeine-containing cough and cold medicines may have a positive impact on the consumer. However, as with Options 1 and 2, it is anticipated that individual health outcomes would continue to deteriorate for consumers who abuse or misuse codeine, and the resulting costs to the healthcare system over time will increase.

Option 4: Up-schedule Schedule 2 to Schedule 4

Under Option 4, current Schedule 2 entries for codeine would be up-scheduled to Schedule 4. The changes and regulatory impacts are summarised in (Table 12). This option will affect 46 ARTG medicine entries (entirely OTC) across 15 sponsors (Table 4, p. 45). The same baseline assumptions have been used as outlined under Option 1.

Table 12: Regulatory impacts of Option 4

	Current	Proposed change	Impact
Distribution model	Schedule 2	Schedule 4	Consumer must see doctor for prescription
Label	Advisory statement(s) as per RASML	Insertion of 'prescription only' medicine	Update of label
Pack Size	6 days' supply	Not prescribed	Nil
Dosage	10 mg per dosage unit, 60 mg per day	No formulation change	Nil
ARTG, CMI and PI	Registered OTC medicine on ARTG	Register prescription medicine on ARTG	ARGPM: Category 1/2 application (Type G or J) including new PI/CMI + GMP conformity assessment (if required for sponsor)

Source: KPMG 2016, Table D11

Regulatory cost assumptions

- There are no packaging or supply restrictions for Schedule 4 products.
- Up-scheduling Schedule 2 medicines to Schedule 4 will require sponsors to apply to register a prescription medicine. Consultations have identified significant commercial and practical barriers to migrating low-dose codeine products to a prescription-only market. Further, it is not clear whether there is a market for former Schedule 2 medicines in this scenario. For this reason it is estimated that only 15% of current Schedule 2 sponsors, would migrate their products to Schedule 4. Due to the need for portfolio rationalisation, it is estimated that each sponsor will migrate two products. As there are currently 15 sponsors with Schedule 2 medicines, the total number of medicines to be carried forward into the model is therefore 4 medicines (15% of 15 sponsors and 2 products per sponsor) which will incur costs to update labels. It has been assumed that each product to be up-scheduled relates to a separate ARTG entry.¹²¹
- Based on BAU costs outlined in Option 1, the label pre-production and production costs are estimated to be \$0.017 million.
- The required changes fall under a major variation (Category 1 application – maximum processing time of 255 days) but TGA have advised that since these applications do not relate to a new chemical entity or a new indication(s) then the actual processing time (and associated data requirements) is likely to be considerably less than that required for a standard Category 1 application. Based on a review of the applicable forms it is estimated that 12 hours will be required to prepare and submit the relevant forms (including the creation of PI and CMI documentation). This estimate assumes that current Schedule 2 sponsors will adopt the efficient practice of replicating the PI documentation of a generic product already in the market. It is also possible that a core PI would be created to assist industry with an efficient migration of these products which would further reduce costs. The

¹²¹ In actuality, the two products for each sponsor might be able to be incorporated into a single ARTG entry but we have left this as each product up-scheduled from Schedule 2 to Schedule 4 requires a separate ARTG entry to avoid understating the regulatory burden.

cost of completing the required form and provision of supporting materials is estimated to be \$0.003 million.

- This analysis has not accounted for reformulation in response to Option 4 as consultation has indicated that, due to costs and potential regulatory barriers to the redeployment of branding, there should be no reformulation.
- Registered prescription (Schedule 4) medicines have the site of manufacture of the active pharmaceutical ingredient(s) [API] recorded in the ARTG. Moving to Schedule 4 will require more detailed ARTG records for the products, with the addition of the site of API manufacture. This is a minor administrative process that can be combined with any other application type (e.g. an application to amend the labels).
- For new prescription medicines, evidence of Good Manufacturing Practice (GMP) at API manufacturing sites is assessed by the TGA. Schedule 2 medicine sponsors currently self-certify that they are compliant with GMP principles; subsidiary GMP requirements encompass supplier (e.g. API) qualification. The TGA can seek evidence of GMP compliance from sponsors of medicines at any time. Sponsors who already have a related Schedule 4 medicine containing codeine made at the same medicine manufacturing site are assumed to be compliant with API GMP requirements and possess all necessary GMP evidence (it is noted that this applies to 3 of the current 15 Schedule 2 sponsors). For other products, where Schedule 2 medicines are converted to Schedule 4 medicines on the ARTG due to the up-scheduling of codeine, the TGA may seek GMP evidence. It is estimated that the engagement of GMP professionals, development of documentation, and implementation of staff and managerial processes would cost \$34,500 per impacted sponsor.
- Similarly for new prescription medicines, the manufacturing process and controls for the API(s) are reviewed. Any up-scheduling is a change to a currently supplied medicine: the extent of review at the time of up-scheduling is a matter of judgement by TGA. The TGA might require assurances from the sponsor that no changes have been made to the existing Schedule 2 products that would move to Schedule 4, including the API manufacturing site(s). If a sponsor changes API details for these products in the future, the required documentation to demonstrate compliance will be required.
- Sponsors who already have a Schedule 4 medicine manufactured at the same manufacturing site are assumed to be compliant with GMP requirements and possess all necessary certification (it is noted that this applies to three of the current 15 Schedule 2 sponsors). As detailed above, 3 sponsors are estimated to undertake this process. The upfront cost of demonstrating GMP compliance is estimated to be \$0.069m.
- The reclassification of Schedule 2 medicines to Schedule 4 will require patients to visit a doctor to obtain a prescription for any product containing codeine. This will increase the compliance burden on individuals. The costs to the healthcare system, in the form of GP payments via MBS, are outside the scope of regulatory modelling as they are considered a direct financial cost and not a compliance cost. These are instead considered in the economic modelling. It is estimated that consumers will require 15 minutes (each way) to drive to their local doctor (therefore a total of 30 minutes). It is also estimated, based on consumer behaviour survey data, that individuals will spend an average of 30 minutes in a waiting room before being able to see their doctor and that they will have a standard 15 minute consult (therefore a total of 1.25 hours).¹²² The time taken for the pharmacist to process the script and talk to the consumer regarding the prescription medicine is estimated to be 2 minute (please note that no adjustment was made in relation to the estimated pharmacist

¹²² www.wsmi.org/wp-content/uploads/2015/06/CONSUMER-BEHAVIOUR-FACT-BOOK-MARCH-2015.pdf

wage rate for whether the processing of the script is undertaken by a pharmacist's assistant rather than the pharmacist as not all pharmacies will have this business model).

- Based on the economic modelling undertaken for this RIS it is estimated that Option 4 will generate an additional average of 200,000 GP appointments per annum over the next ten years. This estimate accounts for the modelled behaviour of consumers in these scenarios (demand side), factors in supply side assumptions, and assumes no repeats due to Schedule 2 codeine medication being indicated for cough and colds. In addition, the economic modelling shows that there are 599,000 per annum existing visits to GPs (that is, would have occurred in the absence of the proposed regulatory change) where a script for codeine would be requested. For the latter category it is assessed that this does not increase the time taken to visit the GP by consumers (as they were undertaking a GP visit anyway) but does result in a slight incremental increase in the duration of the consultation because the GP now needs to prepare a script for codeine (it is assessed that no additional time is required by GPs compared to the average consultation for writing a script for codeine for the additional GP appointments). The increase in the time taken by pharmacists to respond to the regulatory change is the net of the two populations (additional GP appointments plus existing GP appointments with a codeine script requested).

The regulatory cost calculations (RBM) for Option 4 is reported in Table D12 of the KPMG Report (2016) in Annex 1, with the regulatory costs presented below in Table 13. When averaged over ten years the total regulatory cost for Option 4 is \$10.24 million per annum.

Impacts

Impact on the medicines industry

Current sponsors of Schedule 2 products containing codeine would be required to update their labels to reflect the change from Schedule 2 to Schedule 4. All sponsors would need to complete the required documentation to effect the required change to their ARTG entries.

Consultations with industry stakeholders have indicated that rationalisation of current Schedule 2 products is likely to occur with this regulatory option. Some industry members indicated that Schedule 4 product lines would not be feasible as they currently did not have a prescription medicine arm to their business model. This feedback provided support to the assumptions used in determining the regulatory costs associated with this option.

Impact on consumers and healthcare professionals

The change from Schedule 2 to Schedule 4 would require patients to visit a doctor to obtain a prescription for any product containing codeine. This would result in a slight increase in time for doctors to write out the script. The requirement to see a doctor might generate health gains compared with the existing situation by driving changes in treatment and therapy. However in the case of Schedule 2 these gains are expected to be small and were not quantified in the economic model. There is also projected to be a net reduction in out of pocket expenses for the consumer as a consequence of patients substituting the Schedule 2 medicine with another OTC rather than visit their GP for a prescription.

Impact on the government

Increased visits to general practitioners will result in increased costs to MBS, however patients are also expected to incorporate obtaining a prescription with other visits that would otherwise occur.

The present value predicted additional costs to MBS for option 4 for the period of 2017-2026 is \$56.03 million, all relating to GP consultation costs for treatment and source a prescription for low-dose codeine medicine.

Regulatory costs

The average annual regulatory costs (Table 13) for Option 4 are estimated to be \$10.24 million per annum when averaged over ten years.

Table 13: Average annual regulatory costs (from business as usual) for Option 4

Change in costs (\$million)	Business	Community organisations	Individuals	Total change in costs
Total, by sector^{a, b}	2.53	0.00	7.71	10.24

^a From business as usual; ^b Change in costs (\$millions); Source: KPMG 2016, Table D12

Health costs

Under Option 4, current Schedule 2 entries for codeine in cough and cold medicine preparations would be up-scheduled to Schedule 4. The economic health costs are estimated to be \$56.03 million for the period of 2017-2026 (7% discounted), primarily driven increases to MBS for a greater number of GP visits related to treatment and sourcing a prescription.

In addition, consumers will experience out of pocket expenses by purchasing the medicine (time and cost) and seeing their doctor (\$7.71 million).

Some key clinical stakeholders noted that the initial increase in the number of people who are additionally treated and experience a health benefit is likely to decline over a few years until the system recalibrates. That is, patients who are currently using low-dose codeine medicines and who, following up-scheduling, will pursue therapeutic pathways that improve health outcomes, are part of a cohort. They will receive additional treatment and care for the following year, but this additional treatment, compared to what they would otherwise have received, will reduce each year. The economic model captures this factor by assuming, in the base case, a 30% annual reduction on previous year's treatment and health gains. This factor was incorporated into the model by using an average (over ten years) number of additional GP appointments (200,000 additional appointments per year for Option 4 and 51,000 additional appointments per year for Option 6). The additional regulatory compliance costs for doctors and pharmacists are likely to occur over the entire ten-year period used for the regulatory modelling, and is predicted to be \$2.53 million.

The cohort of consumers changing their behaviour from status quo is likely to reduce over time. These additional health costs should be considered in conjunction with the health benefits provided for this option (\$243.95 million) for the same period.

Health benefits

As detailed in the economic model in the KPMG report (2016), some health benefits may be realized by the implementation of Option 4, estimated to be \$243.95 million for the period 2017-2026. The requirement to see a doctor would likely generate health gains compared to the existing situation by driving changes in diagnosis and treatment.

Schedule 2 codeine-containing cough and cold preparations represent the smallest subset of OTC codeine-containing medicines on the market. Hence, the up-scheduling of Schedule 2 (cough and cold) medicines to prescription medicines is likely to lead to an increase in awareness of risks associated with codeine due to health practitioner intervention, but on a lesser scale when compared to Option 6. One significant public health benefit is the exploration of alternative treatment pathways for a persistent cough.

Our targeted stakeholder consultations have indicated that product rationalisation is a likely consequence of this regulatory option and therefore may result in less choice of cough and cold preparations. However, noting that consumers appear to be misinformed of the risks, benefits and proper use of these preparations¹²³, consumers are likely to make an informed choice on how to use such preparations when this information is conveyed to patients at the time of consultation.¹²⁴ On this basis, greater awareness of the risks posed by codeine-containing cough and cold medicines may also encourage conversations about the use of such medicines in relieving symptoms.

In isolation, an up-schedule from Schedule 2 to Schedule 4 is likely to have a small positive effect on health benefits for individuals. Indeed, the economic modelling estimated the health benefit to be \$243.95 million for the period 2017-2016, a small benefit in comparison to Option 6 (\$5,353.17 million). Consumers misusing or abusing codeine-containing medicines in Schedule 2 may shift to Schedule 3 medicines. Hence, for any health benefits to be realised, Option 6 (up-schedule of Schedule 3 medicines to Schedule 4) will need to occur simultaneously with Option 4 to prevent diversion of the misuse problem to Schedule 3 medicines. This is discussed in Scenario 4.

Option 5: Reduce pack size of Schedule 3 and new label warning

Under Option 5 the current Schedule 3 entries for codeine products would be amended to reduce the pack size to not more than 3 days' supply and include a warning label that codeine can cause addiction. The changes and regulatory impacts are summarised in Table 14.

This option will affect 168 ARTG medicine entries (entirely OTC) across 22 sponsors (Table 4, p. 45).

Table 14: Regulatory impacts of Option 5

	Current	Proposed change	Impact
Distribution model	Schedule 3	Schedule 3	Nil
Label	Advisory statement for addiction not required	New advisory statement	Update label
Pack Size	5 days' supply	3 days' supply	Reduce pack size
Dosage	12 mg per dosage unit 100 mg per day	No formulation change	Nil
ARTG, CMI and PI	Registered OTC medicine on ARTG	Update ARTG OTC entry	Updated ARTG entry

Source: KPMG 2016, Table D14

¹²³ <http://www.racgp.org.au/afp/2015/july/self-medication-for-cough-and-%E2%80%A8the-common-cold-information-%E2%80%A8needs-of-consumers/> accessed November 2016

¹²⁴ Johnson G and Helman C (2004) Remedy or cure? Lay beliefs about over the counter medicines for coughs and colds, *Br J Gen Pract*, 54(499):98-102

Regulatory cost assumptions

- As part of industry initiatives several sponsors have recently implemented advisory warnings to warn consumers of codeine addiction. However, some additional labelling changes would likely be required as a result of the reduced pack size. Based on the baseline assumptions, 420 OTC products currently marketed in Australia will be affected.
- As noted in Option 2, it is estimated that half of the product label updates can be rolled into already planned updates reducing the per product cost by 50% for that segment. Therefore the carry forward figure of 210 labels will need to be updated in addition to BAU labelling activities.
- Based on BAU costs outlined in Option 1, the label pre-production and production costs are estimated to be \$0.88 million.
- Consultations have identified that roughly 50% of codeine sponsors already produce 3-day packs or have a production line that could accommodate this change across their product portfolio (provided the implementation timeframe is sufficient). These sponsors will not need to implement new manufacturing arrangements for the outer carton (apart from the printing) nor inner blister pack. It is estimated that approximately 11 sponsors will incur costs to change their pack size.
- It is estimated from industry consultations that up-front costs for the impacted sponsors to implement the required packaging changes is \$30,000 per sponsor. This may include re-tooling to modify blister pack lengths or reduce packaging depth. It should be noted however, that these costs can vary depending on the location of the manufacturing facility being used. For example, changes can be implemented more quickly in domestic facilities but are more expensive, whereas changes in overseas facilities can be implemented at lower cost, but are subject to longer delays due to competing priorities.
- Based on BAU costs outlined in Option 1 and the factors listed above, packaging transition costs are estimated to be \$0.33 million.
- The required changes fall under a C1 application level.¹²⁵ Based on a review of the applicable forms and consultation with sponsors, it is estimated that 6 hours will be required to prepare and submit the relevant form (including updates to the PI and the CMI). The cost of completing the required form is estimated to be \$0.066 million.
- The regulatory cost calculations (RBM) for Option 5 is reported in Table A15 of the KPMG Report (2016) in Annex 1, with the regulatory costs presented below in Table 15.

Impacts

Impact on the medicines industry

Current sponsors of Schedule 3 products containing codeine would be required to update their labels to reflect the reduced pack size and include a new advisory statement that codeine can cause addiction (less those that already contain this advisory statement – currently voluntary). Current sponsors who do not already have a 3-day pack in their production portfolio would need to implement new manufacturing arrangements. All sponsors would need to complete the required documentation to implement the required change to their ARTG entries.

¹²⁵ For more information regarding change applications, see the TGA website at <https://www.tga.gov.au/book-page/step-2-determining-your-application-level-and-change-codes>

Impact on consumers and healthcare professionals

Healthcare professionals are not predicted to be impacted by the implementation of Option 5. Due to the reduction in pack size consumers are expected to spend more to maintain current codeine use. Health gains are not predicted as there is not expected to be any change in treatment or therapy for those consumers currently using low-dose codeine when other therapies might be more effective or as effective but with reduced side effects.

Impact on the government

No impact on government operations are expected for this option.

Regulatory costs

When averaged over ten years the average annual regulatory cost (Table 15) for Option 5 is \$0.13 million; this net regulatory cost accounts for BAU relabelling that occurs frequently. The total regulatory cost for the period 2017-2026 is \$1.3 million.

Table 15: Average annual regulatory costs (from business as usual) for Option 5

Change in costs (\$million)	Business	Community organisations	Individuals	Total change in costs
Total, by sector ^{a, b}	0.13	0.00	0.00	0.13

^a From business as usual; ^b Change in costs (\$millions); Source: KPMG 2016, Table D16

Health costs

Under Option 5 the current Schedule 3 entries for codeine would be amended to reduce the pack size to not more than 3 days' supply and include a label warning that '*codeine can cause addiction*'. The economic health costs are estimated to be \$409.87 million for the period of 2017-2026 (7% discounted), primarily driven by the out of pocket expenses to consumers by purchasing the medicine more frequently due to smaller pack size.

Health benefits

Limited health benefits could be realized by the implementation of Option 5, and these would be principally driven by minor changes in consumer buying behaviour due to the label changes and the reduction pack size. Consumers would need to visit the pharmacy more often to source these medicines due to smaller pack size, leading to an increased probability that consumers will be adequately informed of the risks of codeine and provided alternative products for their specific condition. Given the busy pharmacy environment, and the lack of referral pathways associated with pharmacies, these consultations are unlikely to encourage the exploration of alternative treatment pathways that would be required for significant gains in QALYs. As codeine-containing analgesics will remain available OTC, it is less likely that consumers using codeine for chronic pain will seek advice from GPs. Hence further diagnosis and other treatment options, including referral to a pain management clinic or other non-pharmacological interventions, are less likely to be explored.

Schedule 3 codeine-containing medicines represent the largest subset of low-dose codeine medicines on the market. Reducing the pack size of these products is likely to result in modified behaviour in individuals who are dependent on codeine. For example, '*pharmacy shopping*' is likely to increase as consumers attempt to source codeine.

As detailed in the economic model, no significant health benefits are likely to be realized by the implementation of Option 5. As noted earlier in the report, the only projected health benefits factored into the economic model arose from improved therapeutic pathways taken by patients who are chronic users of low-dose codeine. For an improved therapeutic pathway to be realized the key enabler was a visit to a GP, which will not occur under this option. Given the level of concern for public health and safety, it is anticipated that this option could not occur in isolation of Option 2 (amend Schedule 2 entries to reduce the pack size to not more than 3 days' supply). This is discussed under Scenario 3 (p. 88).

Therefore, if Option 5 is implemented it is anticipated that individual health outcomes would not improve for consumers who abuse or misuse codeine, and the resulting costs to the health care system over time will increase.

Option 6: Up-schedule Schedule 3 to Schedule 4

Under Option 6, current Schedule 3 entries for codeine would be up-scheduled to Schedule 4 and current Schedule 4 and 8 entries for the Poisons Standard would be amended to reflect this change. The changes and regulatory impacts are summarised in Table 16.

This option will affect 168 ARTG medicine entries (entirely OTC) across 22 sponsors (Table 4, p. 45).

Table 16: Regulatory impacts of Option 6

	Current	Proposed change	Impact
Distribution model	Schedule 3	Schedule 4	Consumer must see doctor for prescription
Label	Advisory statement(s) as per RASML	Insertion of 'Prescription Only' medicine	Update of label
Pack Size	5 days' supply	Not prescribed	Nil
Dosage	12 mg per dosage unit 100 mg per day	No formulation change	Nil
ARTG, CMI and PI	Registered OTC on ARTG	Register prescription medicine on ARTG	ARGPM: Category application (Type G/J) including new PI/CMI + GMP conformity assessment (if required for sponsor)

Source: KPMG 2016, Table D17

Regulatory cost assumptions

- The packaging options (reduced pack size and mandatory warning statements) are not relevant to Schedule 4 products, as prescription medicines already have packaging restrictions.
- Up-scheduling Schedule 3 products to Schedule 4 will require sponsors to apply to register a prescription medicine. It is estimated that 50% of current Schedule 3 sponsors will seek to migrate their products to Schedule 4. Further, it is estimated that Schedule 3 sponsors will rationalise their portfolio to two products per sponsor given the challenging commercial realities of the prescription-only market. As there are currently 22 sponsors of Schedule 3

products, the total number of products to be carried forward into the model is therefore 22 medicine products (50% of 22 sponsors (therefore 11 sponsors) and 2 products per sponsor) which will incur costs to update labels. It has been assumed that each product to be up-scheduled relates to a separate ARTG entry.¹²⁶

- Based on BAU costs outlined in Option 1, the label pre-production and production costs are estimated to be \$0.092 million.
- The required changes fall under a minor variation (Category 3 application) level. Based on a review of the applicable forms, it is estimated that 4 hours will be required to prepare and submit the relevant form. The cost of completing the required form is estimated to be \$0.005 million.
- This analysis has not accounted for reformulation as consultation has indicated there will be no reformulation in response to Option 6 due to costs and potential regulatory barriers to the redeployment of branding.
- As outlined in Option 4, registered prescription (Schedule 4) medicines have the site of manufacture of the active pharmaceutical ingredient(s) [API] recorded in the ARTG. Moving to Schedule 4 will require more detailed ARTG records for the products, with the addition of the site of manufacture of the API. This is a minor administrative process which can be combined with any other application type (e.g. an application to amend the labels).
- For new prescription medicines, evidence of Good Manufacturing Practice (GMP) at API manufacturing sites is assessed by the TGA. Schedule 3 sponsors currently self-certify that they are compliant with GMP principles; subsidiary GMP requirements encompass supplier (e.g. API) qualification. The TGA can seek evidence of GMP compliance from sponsors of medicines at any time. Sponsors who already have a related Schedule 4 medicine containing codeine made at the same medicine manufacturing site are assumed to be compliant with API GMP requirements and possess all necessary GMP evidence (it is noted that this applies to 3 of the current 22 Schedule 3 sponsors). In addition, 14 of the remaining 22 Schedule 3 sponsors also have a product in Schedule 2. To avoid double counting with Option 4, it is assumed that only 3 sponsors¹²⁷ will incur costs to obtain GMP certification from the TGA. Where Schedule 3 medicines are converted to Schedule 4 medicines on the ARTG due to the up-scheduling of codeine, the TGA may seek GMP evidence. It is estimated that the engagement of GMP professionals, development of documentation, and implementation of staff and managerial processes would cost \$34,500 per impacted sponsor.
- Similarly for new prescription medicines, the manufacturing process and controls for the API(s) are reviewed. Any up-scheduling is a change to a currently supplied medicine: the extent of review at the time of up-scheduling is a matter of judgement. The TGA might require assurances from the sponsor that no changes have been made to the existing Schedule 2 products that would move to Schedule 4, including the API manufacturing site(s). If a sponsor changes API details for these products in the future, the required documentation to demonstrate compliance will be required.

¹²⁶ In actuality, the two products for each sponsor might be able to be incorporated into a single ARTG entry but we have left this as each product up-scheduled from Schedule 2 to Schedule 4 requires a separate ARTG entry to avoid understating the regulatory burden.

¹²⁷ The figure was calculated as follows: Currently 22 Schedule 3 sponsors. 3 of these sponsors also have Schedule 4 products (carry-forward figure is 19). 14 of the remaining Schedule 3 sponsors also have Schedule 2 drugs (and so are picked-up in Option 4 calculations) which leaves 5 remaining sponsors. If we assume that the 50% of Schedule 3 sponsors indicated by industry consultations that are likely to migrate products from Schedule 3 to Schedule 4 are wholly contained within this group, then this leaves a maximum of 3 sponsors.

- It is estimated that the engagement of GMP professionals, development of documentation, and implementation of staff and managerial processes would cost \$34,500 per impacted sponsor.
- The reclassification of Schedule 3 products as Schedule 4 will require that patients visit a doctor to obtain a prescription for any analgesic product containing codeine. This will increase the compliance burden on individuals. As noted in Option 4 this will require 1.33 hours to travel to and from a doctor's, attend an appointment, and then visit a pharmacy to obtain the medicine. As per Option 4, it is also assumed doctors spend an additional 30 seconds to process the prescription for these new visits and that pharmacists will take an additional 1 minute to process the script and talk to the consumer when providing them the medicine.
- Based on the economic and social impact modelling undertaken for this RIS it is estimated this option will generate an additional average of 51,000 GP appointments per annum over the next ten years. This estimate accounts for the modelled behaviour of consumers in these scenarios (demand side), factors in supply side assumptions, and assumes a maximum of five repeats (therefore up to 6 packs per script). In addition, the economic modelling shows that there are 152,000 existing visits to GPs (that is, would have occurred in the absence of the proposed regulatory change) where a script for codeine would be requested. For the latter category it is assessed that this does not increase the time taken to visit the GP by consumers (as they were undertaking a GP visit anyway) but does result in a slight incremental increase in the duration of the consultation because the GP now needs to prepare a script for codeine ((it is assessed that no additional time is required by GPs compared to the average consultation for the writing of script for codeine for the additional GP appointments). As this option relates to up-scheduling Schedule 3 to Schedule 4 there is assessed to be no additional time required by pharmacists (assuming a 2 minute time interaction for the processing of Schedule 3 transactions).
- The regulatory cost calculations (RBM) for Option 6 are reported in Table A18 of the KPMG Report (2016) in Annex 1, with the regulatory costs presented below (Table 17).

Impacts

Impact on the medicines industry

Current sponsors of Schedule 3 products with codeine as the active ingredient would be required to update their labels to reflect the change from Schedule 3 to Schedule 4. All sponsors would need to complete the required documentation to effect the required change to their ARTG entries.

Impact on consumers and healthcare professionals

The change from Schedule 3 to Schedule 4 would require patients to visit a doctor to obtain a prescription for any product containing codeine. This would result in a slight increase in time for doctors to write the script. The requirement to see a doctor would likely generate health gains compared to the existing situation by driving changes in treatment and therapy. Also predicted is a net reduction in out of pocket expenses for the consumer as a consequence of patients substituting the Schedule 3 medicine with an OTC rather than visit a GP for a prescription.

Impact on the government

An increase in the number of GP visits will result in an increase in MBS costs. For some patients however, there will be a health gain if they access cost effective therapies, including more suitable prescription medicines or specialist referrals for pain management.

Regulatory costs

The average annual regulatory costs for Option 6 (Table 17) are estimated to be \$2.21 million per annum when averaged over ten years. The total regulatory costs for the period of 2017-2026 is \$22.10 million (not discounted).

Table 17: Average annual regulatory costs (from business as usual) for Option 6

Change in costs (\$million)	Business	Community organisations	Individuals	Total change in costs
Total, by sector^{a, b}	0.24	0.00	1.97	2.21

^a From business as usual; ^b Change in costs (\$million); Source: KPMG 2016, Table D19

Health costs

Under Option 6, current Schedule 3 entries for codeine would be up-scheduled to Schedule 4. The economic health costs, estimated to be \$209.87 million for the period of 2017-2026, are primarily driven by out of pocket expenses for consumers as a result of purchasing the medicine and making an appointment to see their doctor.

Health benefits

As detailed in the economic model, substantial health benefits (\$5,353.17 million for the period of 2017-2026, 7% discounted) will be realized by the implementation of Option 6. The only projected health benefits factored into the economic model arose from improved therapeutic pathways including changes in treatment and therapy in patients who are chronic users of low-dose codeine medicines. For this improved therapeutic pathway to be realized, the key enabler was a visit to a GP, which is highly likely to occur under this option. It is anticipated that this option could not occur in isolation of Option 4 (Schedule 2 entries would be up-scheduled to Schedule 4). This is discussed under Scenario 4 (p. 88).

Schedule 3 codeine-containing medicines represent the largest subset of codeine-containing OTC medicines on the market. If low-dose codeine-containing analgesics are no longer available OTC in pharmacies, it is more likely that patients using codeine for chronic pain will seek advice from GPs. Hence further diagnosis and other treatment options, including referral to a pain management clinic or other non-pharmacological interventions, are more likely to be explored, and quality of life years (QALY) gains are realised. The broad options for acute and chronic users of Schedule 3 codeine products and their relationship to potential health benefits under Option 6 are illustrated in Figure 5.

The substantial health benefits are driven by the gain in QALY of 9,208 in 2017 as patients receive treatment they would otherwise not have accessed that leads to more effective therapy compared to low-dose codeine combination medicines. This gain is offset by the QALY loss of 134 experienced by a small proportion of clients for whom low-dose codeine combination medicines are the most effective option available to them and who do not attend a GP to obtain a prescription under Scenario 4. This situation was identified by some stakeholders. Systematic

reviews indicate¹²⁸ that, on average, current acute users and chronic users of low-dose codeine combination medicines who change to OTC only paracetamol and/or ibuprofen will experience no change in pain relief and hence do not experience a QALY loss.

The monetary valuation of a QALY (\$182,000) was used to ensure consistency with OBPR guidelines.¹²⁹ This resulted in a gain of \$1,651.5 million (in 2017) and a gain (present value) of \$4,399.5 million over 2017-26. The ten year result is not simply ten times the first year result, as the majority of the QALY gains occur in the first two years as customers pursue different options as a consequence of attending a GP consultation. Stakeholders stated that this initial activity would reduce over time. The model assumes the reduction in the number of patients participating in additional therapy occurs at a rate of 30% per year. (The QALY gained is assumed conservatively to occur only in the year that treatment occurs).

Some health benefits associated with dependent users may not be realised due to abusers of codeine entering into '*doctor shopping*' behaviour. However, the potential increase in this type of behaviour may be offset by raising awareness through an education campaign and encouraging best prescribing practices with GPs. Further, dependent users of codeine may divert to other readily available substances (other medicines or illegal substances) to provide relief to their addiction.

The positive net benefit for Option 6 is robust to a wide range of sensitivity analyses, including:

- Number of deaths prevented;
- the costs of gaining any quality of life improvements through improved treatment for chronic pain, for example, are increased by 80%; and
- the quality of life gain from treatment is reduced by 80%.

The variables that net benefit was most sensitive to were the average QALY gain resulting from additional treatment received and the number of repeat scripts. The result was only moderately sensitive to the discount rate, number of deaths prevented, and the co-payment for GP and specialist consultations.

The economic modelling accounts for additional health costs such as out-of-pocket expenses for consumers cost to the MBS through increased GP and/or specialist consultations and the additional costs to the Government (MBS and PBS; see net benefit for scenarios). These health costs are assumed to begin 12 months after a scheduling decision is made.

¹²⁸ Cochrane reviews are systematic reviews of primary research in human health care and health policy, and are internationally recognised as the highest standard in evidence-based health care resources. See <www.cochrane.org/whjat-is-cochrane-evidence>. Relevant reviews are: Derry S, Moore RA, McQuay HJ. Single dose oral codeine, as a single agent, for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2010, Issue 4. Art. No.: CD008099. DOI: 10.1002/14651858.CD008099.pub2. Toms L, McQuay HJ, Derry S, Moore RA. Single dose oral paracetamol (acetaminophen) for postoperative pain in adults. Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD004602. DOI: 10.1002/14651858.CD004602.pub2. Derry CJ, Derry S, Moore RA, McQuay HJ. Single dose oral ibuprofen for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD001548. DOI: 10.1002/14651858.CD001548.pub2. Toms L, Derry S, Moore RA, McQuay HJ. Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD001547. DOI: 10.1002/14651858.CD001547.pub2. Derry S, Karlin SM, Moore RA. Single dose oral ibuprofen plus codeine for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2015, Issue 2. Art. No.: CD010107. DOI: 10.1002/14651858.CD010107.pub3. Derry CJ, Derry S, Moore RA. Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD010210. DOI: 10.1002/14651858.CD010210.pub2.

¹²⁹ Office of Best Practice Regulation, 'Best Practice Regulation Guidance Note: Value of statistical life', dated December 2014.

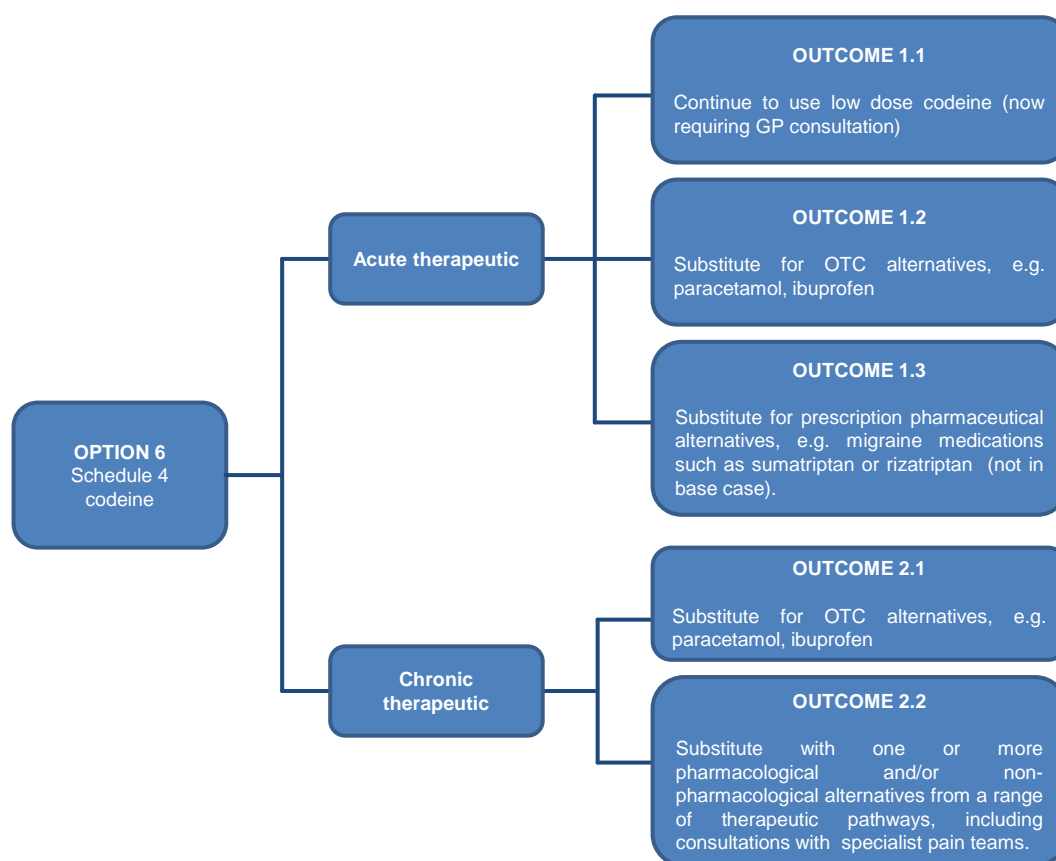


Figure 5: Option 6 outcomes for acute and chronic users of current Schedule 3 codeine

Acute users are the only consumer group expected to have some users who continue to use low-dose codeine at the same rate over the ten years of the model (Outcome 1.1). This assumption is based on discussions with stakeholders, some of whom indicated that it was unlikely that GPs would continue to prescribe low-dose codeine for chronic users. Stakeholders instead indicated that GPs would likely prescribe higher dose codeine, or a range of other therapeutic options that may not have been otherwise suggested (Outcomes 1.3 and 2.2) had the consumer not seen a GP and instead continued to use OTC low-dose codeine. These are the outcomes that could result in health gains for consumers.

Therefore, if Option 6 is implemented, it is anticipated that individual health outcomes would improve for consumers who abuse or misuse codeine, and the related costs to the healthcare system over time will decrease.

Regulatory burden estimate (RBE) for each option

Table 18 shows the regulatory costs for each of the six specified options separated into the stakeholder types: business, community organisations and individuals.

Table 18: Average annual regulatory costs (from business as usual) by sector for all options

	Change in costs (\$million)	Business	Community Organisations	Individuals	Total change in costs (\$million)
Option 1	Status quo	0	0	0	0
Option 2	Reduced pack size and new label warning for Schedule 2 products	0.05	0	0	0.05
Option 3	Schedule 2 to Schedule 3, reduced pack size and new warning label)	6.95	0	3.19	10.14
Option 4	Schedule 2 to Schedule 4	2.53	0	7.71	10.24
Option 5	Reduced pack size and new label warnings for Schedule 3 products	0.13	0	0	0.13
Option 6	Schedule 3 to Schedule 4	0.24	0	1.97	2.21

Regulatory burden estimate (RBE) for each scenario

Although the regulatory costs outlined in Table 18 above were calculated for six specified options for the purpose of inclusion in the RIS, there is a logical grouping of options, resulting in four scenarios (see Table 2 for summary of scenarios). The average annual regulatory burden estimates (RBE) for each scenario is given in Table 19. In accordance with OBPR requirements, the costs outlined in Table 19 have been calculated for a 10-year period and presented as an average annual amount. It is worth noting that there are assumptions and limitations underpinning the regulatory impact analysis, and the conclusions of the analysis should be regarded as indicative rather than definitive. Assumptions have been made based on general information, ARTG data on existing products, stakeholder feedback, and data provided by the broader Department of Health (specifically the Medical (MBS) and pharmaceutical benefits (PBS) divisions).

Table 19: Average annual regulatory costs (from business as usual) by sector for all scenarios.

	Change in costs (\$million)	Business	Community Organisations	Individuals	Total change in cost
Scenario 1	Option 1 (status quo)	0	0	0	0
Scenario 2	Options 2 and 5 (Schedules 2 and 3 reduced pack size and new label warning)	0.18 (0.05 + 0.13)	0	0	0.18
Scenario 3	Options 3 and 5 (Schedule 2 to Schedule 3, reduced pack size and new warning label)	7.08 (6.95 + 0.13)	0	3.19 (3.19 + 0)	10.27
Scenario 4	Option 4 and 6 (Schedules 2, 3 to Schedule 4)	2.77 (2.53 + 0.24)	0	9.68 (7.71 + 1.97)	12.45

Net benefit for each scenario

As stated earlier, a simultaneous modification of the regulatory control mechanisms for both Schedule 2 and Schedule 3 codeine medicines is required. If a single regulatory option was enacted the desired outcomes would largely be negated by consumers shifting from either Schedule 2 to Schedule 3 (or vice versa). By coupling the 6 options, 3 scenarios result (in addition to scenario 1 - status quo). Table 20 details the regulatory cost, health economic costs and benefits per scenario.

For consumers and the government the main additional economic costs relate to:

- net out-of-pocket costs to consumer;
- additional costs to MBS due to additional GP and pain consultations; and
- additional costs to the PBS due to additional scripts for PBS listed pain medications.

The additional costs to the MBS are the primary driver of additional costs to government, while the identified health benefits are principally associated with:

- prevention of accidental death;
- improved quality of life when a patient benefits from other treatment options that would not have previously been explored;
- prevention of adverse events related to unintentional overdose of paracetamol or ibuprofen; and
- reduced dependence and risk of dependency.

Table 20: Regulatory (for first year, 2017 and the period 2017-2026) as well as the economic costs and benefits (for the period 2017-2026) for each option and scenario (\$million)

		Scenario 2		Scenario 3		Scenario 4	
		Option 2	Option 5	Option 3	Option 5	Option 4	Option 6
Regulatory costs (average annual)	Option	(\$0.05)	(\$0.13)	(\$10.14)	(\$0.13)	(\$10.24)	(\$22.21)
	Scenario	(\$0.18)		(\$10.27)		(\$12.45)	

For the 10-year period from 2017-2026 the following costs and benefits have been estimated:

Regulatory costs (not discounted)	Option	(\$0.50)	(\$1.30)	(\$101.40)	(\$1.30)	(\$102.40)	(\$22.10)
	Scenario	(\$1.80)		(\$102.70)		(\$124.50)	
Health economic costs (7% discounted)	Option	(\$20.70)	(\$409.87)	(\$14.49)	(\$409.87)	(\$56.03)	(\$209.87)
	Scenario	(\$430.57)		(\$424.36)		(\$265.90)	
Health economic benefits (7% discounted)	Option	0	0	0	0	\$243.95	\$5,353.17
	Scenario	0		0		\$5,597.12	
Net benefit (7% discounted)	Option	(\$21.20)	(\$411.17)	(\$115.89)	(\$411.17)	\$85.52	\$5,121.20
	Scenario	(\$432.37)		(\$527.06)		\$5,206.72	

The regulatory costs as well as the economic costs and net benefits have been derived using two separate models. Each model has inherent assumptions that were informed by specific data or feedback from stakeholder consultations. There were some assumptions in the economic model that had data gaps and conservative estimates have been used in these circumstances. These conservative assumptions using limited data have been clearly articulated in the KPMG report (Annex 1), hence the above are estimates only.

The implementation of Scenario 4 clearly results in a net benefit to society over 10 years (\$5,207 million) (Table 20).

Scenario 1 (Option 1: status quo)

This scenario represents the status quo and hence it is not expected to provide any additional regulatory burden or benefit. However, while there are no net benefits associated with this option, the identified negative net health benefits are significant and should not be dismissed.

While codeine-containing medicines remains in the OTC market, there is no ability for GPs to monitor patient use of codeine for chronic pain, despite GPs being better equipped than pharmacists to do so. Hence other treatment or therapy options for a particular patient are unlikely to be explored or encouraged. On this basis, it is anticipated that individual health outcomes will not improve and, more broadly, the impacts on the healthcare system will continue to increase as they have done so over the last few years.

Furthermore, without reducing the pack size to not more than 3 days' supply and including a label warning that '*codeine can cause addiction*', no change in patient behaviour will likely result in codeine-dependent individuals.

Given the level of concern for public health and safety, this regulatory option could not occur in conjunction with a voluntary real time monitoring (RTM) system that monitors the sale and provision of these medicines [notwithstanding the significant limitations and concerns that have been raised as outlined in '*Why are regulatory options being considered?*' (p. 37)].

Pharmacists would experience increased engagement with '*challenging*' patients when managing the use of OTC codeine medicines, noting that the pharmacy environment does not usually allow for private conversations in the way that doctors' rooms do.

Scenario 2 (Options 2 and 5: reduce pack size of Schedule 2 and Schedule 3 and new label warning)

Scenario 2 (Options 2 and Option 5: reduce the pack size to not more than 3 days' supply on all Schedule 2 and 3 codeine-containing medicines and include a label warning that '*codeine can cause addiction*') is likely to induce some behavioural changes in certain individuals who are dependent or who abuse codeine. Behaviours such as '*Pharmacy shopping*' is likely to increase, as dependent users attempt to source their codeine. Historically, changing the labelling and decreasing the pack size of codeine medicines has not adequately addressed the problem of misuse, dependence or medicine misadventure.

This scenario will affect 214 ARTG medicine entries (entirely OTC) across a total of 37 sponsors (Table 4, p. 45) (22 plus 15).

Table 20 summarises the regulatory burden estimates, economic costs and benefits for Option 2 plus Option 5 to give a negative net benefit of \$432.37 million for this scenario. Other than Scenario 1, this scenario induces the lowest net regulatory and health economic costs of \$1.8 million and \$430.57 million respectively for the period of 2017-2026. The principal economic costs are associated with out-of-pocket costs to consumers.

As for Scenario 1 above, given the level of concern for public health and safety, it is anticipated that regulatory Scenario 2 can not occur in isolation of a mandatory real time monitoring (RTM) system (see p. 37 '*Why are regulatory options being considered?*'). With any adoption of a RTM system, the states and territories will need to agree to support such a mandatory reporting system with changes to relevant jurisdiction legislation which will take time.

As Scenario 2 allows for the continued supply of OTC codeine medicines that have the potential to induce dependency, its adoption will not address all the public health concerns. Furthermore, the current SPF implies that OTC medicines should not require a recording and monitoring system to protect public health, as this is often attributed to Schedule 8 medicines (Controlled Drugs, or drugs of dependence). Hence this scenario would not address the current inconsistency in the scheduling of OTC codeine-containing medicines in Australia, and with the exception of the UK, this would be in contrast to international best practice regulation.

As discussed above (p. 43 '*Business-as-usual (BAU) variations to existing medicines*'), regular changes to medicine labels are part of normal business practice. It is estimated that more than half of the medicines labels for those medicines marketed in Australia are changed every 3 years. When proposing scheduling options for the length of transition time, the burden placed on businesses is consistent with the risks posed to public health.

Furthermore, as stated above under '*Regulatory cost assumptions for Option 2*' (p. 64) from our industry consultations, 50% of codeine sponsors already produce 3 day packs or have a production line that could accommodate this change across their impacted product portfolio, provided the implementation timeframe is sufficient. These sponsors will not need to implement

new manufacturing arrangements for the outer carton (apart from the printing) nor inner blister pack. It is estimated that approximately 18 sponsors (50% of 37 sponsors) will incur costs to change their pack size.

Consultations have indicated that the shortest implementation time frame would be 9 months.

Scenario 3 (Options 3 and 5: up-schedule Schedule 2 to Schedule 3 and reduce pack size for Schedule 3)

Scenario 3 (Option 3 and Option 5: up-schedule Schedule 2 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*') is likely to induce behavioural changes in certain individuals who are dependent or who abuse codeine medicines. Behaviours such as '*Pharmacy shopping*' are likely to increase, as dependent users attempt to source their codeine more often due to the reduced pack size. Historically, changing the labelling and decreasing the pack size of codeine medicines has not adequately addressed the problem of misuse, dependence or medicine misadventure.

This scenario will affect 214 ARTG medicine entries (entirely OTC) across 37 sponsors (Table 4, p. 45) (22 plus 15).

Table 20 shows the summary of the regulatory burden estimates, economic costs and benefits for Options 3 and 5. The net regulatory and economic costs for Scenario 3 are \$102.7 million and \$424.36 million respectively for the period from 2017-2026. The principal economic costs are associated with out-of-pocket costs to consumers. This is attributed to the increased expense of codeine-containing medicines due to pharmacy oversight.

As with Scenario 2, it is anticipated that this regulatory scenario (Options 3 and 5) could not occur in isolation of a voluntary real time monitoring (RTM) system (see p. 37 '*Why are regulatory options being considered?*'). However the costs/benefits of a monitoring system, with all of the the issues highlighted above, have not been modelled.

As for Scenario 2 and discussed above (p. 43 '*Business-as-usual (BAU) variations to existing medicines*'), regular changes to medicine labels are part of normal business practice. It is estimated that more than half of medicines labels for medicines marketed in Australia are changed every 3 years. When proposing scheduling options for the length of transition time, the burden placed on businesses is consistent with the risks posed to public health.

Furthermore, as stated above under '*Regulatory cost assumptions for Option 3*' (p. 68), from our industry consultations, 50% of codeine sponsors already produce 3 day packs, or have a production line that could accommodate this change across their impacted product portfolio, provided the implementation timeframe is sufficient. These sponsors will not need to implement new manufacturing arrangements for either the outer carton (apart from the printing) or inner blister pack. It is estimated that approximately 18 sponsors (50% of 37 sponsors) will incur costs to change their pack size.

Consultations have indicated that the shortest implementation time frame would be 9 months.

Scenario 4: (Options 4 and 6: OTC codeine not available)

When Option 4 is taken together with Option 6 (Scenario 4), all Schedule 2 and Schedule 3 codeine-containing medicines will be up-scheduled to Schedule 4. This scenario will affect 214 ARTG medicine entries (entirely OTC) across 37 sponsors (Table 4, p. 45).

Table 20 summarises the regulatory burden estimates, economic costs and benefits for Options 4 and 6. The predicted net regulatory and economic costs for Scenario 4 are \$124.50 million and \$265.90 million respectively for the period of 2017-2026. The principal economic costs are

associated with out-of-pocket costs to consumers, pharmacies and doctors and increased PBS and MBS costs to the government (discussed below). The economic health benefit is estimated to be \$5,597.12 million for 2017-2026, with a net health benefit of \$5,206.72. The economic health benefits are principally driven by the QALY gains (as described under option 6 above), as better diagnosis and other treatment options are explored, including referral to a pain management clinic or other non-pharmacological interventions.

Behaviours such as '*Pharmacy shopping*' will cease, but dependent users would likely engage in '*doctor shopping*' in an attempt to source their codeine. This is the preferred scenario, as GPs are well equipped to understand the available options to treat these patients.

Codeine-containing medicines are likely to be used for their intended purposes only, with the risks of use clearly articulated at the time of prescribing. Alternative options can be discussed to minimise the risk to patients and increase the quality use of medicines.

For some consumers, Scenario 4 will result in a reduction in out of pocket costs with no change in health status. These consumers are those who currently use low-dose codeine combination medicines occasionally (only three days at a time for acute pain), and are expected to substitute this medicine with codeine free alternative that do not require a prescription. Generally these will be at a lower cost to the consumer compared to the expenditure that would otherwise have occurred, for a medicine that is as effective. Hence there will be financial savings to some consumers as they switch to less expensive medications, without a loss in pain relief.

The identified health benefits of this scenario are:

- prevention of accidental death
- improved quality of life as a patient benefits from other treatment options that would not have previously been explored
- prevention of adverse events related to unintentional overdose of paracetamol or ibuprofen, and
- reduced dependence and risk of dependency.

As with previous scenarios there was a net reduction in out of pocket costs to the consumer. When this occurs, the model adjusts the resultant saving to be included as a benefit, not a negative cost. This saving to consumers is the result of a combination of factors, including:

- the reduction in use of low-dose codeine
- the substitution of low-dose codeine with cheaper supermarket products such as paracetamol or ibuprofen
- patients who continue with prescription medicines (whether containing codeine or not) in most cases will pay the same or less than their current expenditure on low-dose OTC codeine medicines
- if patients substitute low-dose codeine medicine with high dose prescription codeine medicine via script, they can be provided with up to five repeats by their GP, thus reducing the need for visits to their GP
- high bulk-billing rate for GP consultations
- the rate at which pain-related GP consultations can be accommodated within visits that would otherwise have occurred in the absence of the proposed regulatory change.

Consultations have indicated that the shortest implementation time frame for Scenario 4 would be 12 months.

Predicted costs to deliver health benefits

Other economic costs to the government for this scenario relate to additional costs to MBS due to additional GP and pain consultations and additional costs to the PBS due to additional scripts for PBS listed pain medications.

The additional MBS costs in 2017 are estimated at \$59.4 million, of which 83% relate to the costs of improved treatment for pain relief that would otherwise not have occurred. The remainder (\$5.6 million) relate to the costs of additional consultations to obtain prescriptions for low-dose codeine medications. The present value of additional costs to the MBS over the ten-year period 2017-26 are \$185.2 million, of which 61% relate to treatment costs. This difference in the proportion that relate to treatment costs over the ten-year period is the result of the need for treatment for patients with chronic therapeutic use (dependent and non-dependent) decreasing as the use of low-dose codeine medications reduces due to the requirement for patients to obtain a prescription from a GP.

The predicted additional prescription medicines dispensed is 4.6 million with a predicted cost to the PBS (\$23.1 million) in the first year (2017), and the present value of the additional costs to the PBS (\$61.4 million discounted at 7%) over 2017-26 (Table ES11 of the KPMG report). Only some of the 4.6 million additional prescriptions in 2017 that are expected to occur under Scenario 4 will incur cost to the PBS.

Unlike the regulatory costs for industry, the additional costs for doctors and pharmacists are likely to occur over the entire 10-year period and are estimated to be \$2.7 million for Scenario 4 during the period of 2017-2026.

The identified regulatory benefits of this scenario are:

- codeine is scheduled in a manner than provides greater consistency with the SPF (Scheduling Policy Framework), with reduced public risks, and
- Australian regulation of codeine will be consistent with comparable international regulators.

Health benefits

The economic modelling accounts for additional health costs such as out-of-pocket expenses for consumers cost to the MBS through increased GP and/or specialist consultations and the additional costs to the Government (MBS and PBS). These health costs are assumed to begin 12 months after a scheduling decision is made.

The health benefits estimated for Scenario 4 include gains in 'quality of life years' (QALY) due to the exploration of alternative, more effective treatment pathways that would not have previously been explored as well as the prevention of deaths.

The number of deaths prevented per year for Scenario 4 is conservatively estimated at five, based on information derived from the Roxburgh study¹³⁰ with each death prevented valued at \$4.2 million.

A gain in QALY of 9,208 in 2017 was estimated. The monetary valuation of a QALY as per OBPR guidelines¹³¹ is \$182,000, which results in an estimated gain of \$1,651 million (in 2017) and a gain (present value) of \$4,399 million over the period of 2017-26. The majority of the QALY gains occur in the first two years as customers pursue different treatment pathways as a

¹³⁰ Roxburgh A, Hall WD, Burns L, Pilgrim J, Saar E, Nielsen S and L Degenhardt. Trends and characteristics of accidental and intentional codeine overdose deaths in Australia. *Med J Aust* (2015) 203(7).

¹³¹ Office of Best Practice Regulation, 'Best Practice Regulation Guidance Note: Value of statistical life', dated December 2014.

consequence of GP consultation. The model assumes that the reduction in the number of patients participating in additional therapy occurs at a rate of 30% per year.

The health benefits are driven by QALY gains as better diagnosis and other treatment pathways for chronic pain are explored, including referral to pain management clinics or other non-pharmacological interventions. There are predicted economic costs that will be incurred with the delivery of these public health benefits that are principally associated with out-of-pocket costs to consumers, pharmacies/doctors as well as increased PBS and MBS costs to the government.

Overview of consultation activities

Consultation activities included receiving expert advice and recommendations from members of the Advisory Committee on Medicines Scheduling (ACMS), three formal invited public consultations following announcements of scheduling proposals on the TGA website and meetings with other internal stakeholders at the Department of Health.

In addition to formal public submissions made to the TGA regarding the re-scheduling of codeine, targeted formal consultation activities were held with stakeholders including five pharmaceutical companies, four peak bodies, and GPs.

Expert advice from Advisory Committee on Medicines Scheduling

The ACMS comprises independent experts as well as state and territory representatives who provide advice to the medicines scheduling delegate. The ACMS considered codeine re-scheduling at the July 2015 and March 2016 meetings.

At the meeting of the ACMS on 15 March 2016, the interim decision from 1 October 2015 to up-schedule codeine was reconsidered, including all of the public submissions and the external reports and evaluations. The committee also considered the alternative options including the reduction of pack sizes and label advisory statements, which were provided for public comment on 10 December 2015. The ACMS advice in March 2016 was consistent with the advice in August 2015.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* that can be considered by the committee included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The ACMS recommended deletion of the current Schedule 2 and Schedule 3 entries for codeine, and that all codeine-containing products should be in Schedule 4 (prescription-only medications). Their reasons included:

- A greater risk of medication misadventure, dependence and deliberate misuse/abuse while also having a relative lack of efficacy compared to safer products. Changing the labelling and decreasing the pack size was considered to not adequately address these concerns
- OTC products are intended for the management of acute self-limiting pain, however, there is evidence of inappropriate use of OTC codeine for chronic pain
- 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

- Increasing amount of evidence of harm from abuse
- Misuse of OTC codeine products including deaths resulting from hepatic injury, gastrointestinal perforations, hypokalaemia and respiratory depression
- Minimal benefit of OTC products containing codeine compared to the risk profile, which raised broader questions regarding the role of codeine in clinical practice, and
- To adequately determine the clinical needs of the patient suffering chronic or severe pain, an appropriately qualified medical practitioner should assess risk.

Formal consultation periods regarding the re-scheduling of codeine

Extensive public consultation is a critical and legislated component of the process and is associated with scheduling decisions and proposals that would change the Poisons Standard.

If a scheduling proposal is referred to an Advisory Committee then there will be two public consultation periods with invitations announced on the TGA website: a pre-meeting public consultation period and an interim decision public consultation period. The pre-meeting consultation period invites public submissions prior to the Advisory Committee meeting where they are considered by the Advisory Committee. Once the delegate makes an interim decision, this is published on the TGA website, and further public submissions are invited during the interim decision consultation period.

The public consultation process for codeine included an additional public consultation step in December 2015, following public feedback on the interim decision. This allowed for a more thorough consideration of the numerous submissions and broader implications to current products on the market. As part of the additional public consultation period, submitters were asked to comment on other options such as a reduction in pack size and the inclusion of a warning statement on the packaging.

Figure 6 compares the normal public consultation process (on the left) and the one that occurred for codeine (on the right), and provides a timeline of where the consultation periods fit in with the major codeine re-scheduling decision points.

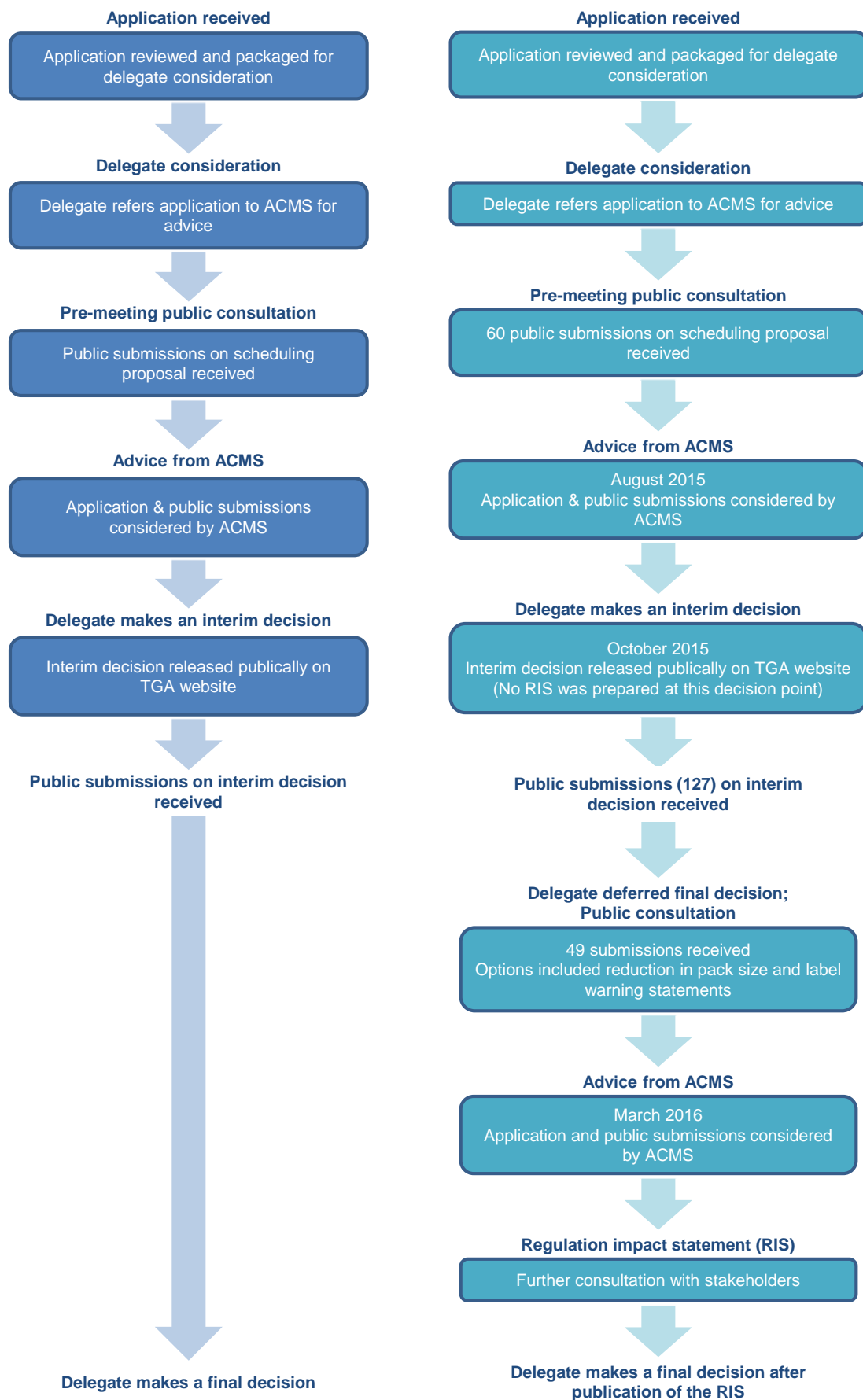


Figure 6: Public consultation process for codeine and the timeline of major decision points
Left, normal consultation process; right, public consultation periods

Pre-meeting (July 2015 ACMS meeting) public consultation

On 1 April 2015, under subsection 42ZCZK/42ZCZL of the *Therapeutic Goods Regulations 1990* (the Regulations), the delegate published a [pre-meeting public notice](#) on the TGA website which specified the proposed amendments to the current Poisons Standard and invited public comment. The proposed amendments referred to the ACMS by the medicines scheduling delegate for codeine were:

- To delete the Schedule 3 entry for codeine, and re-schedule the current Schedule 3 codeine entry to Schedule 4 due to potential issues of morbidity, toxicity and dependence.
- Consideration may be given as to whether all current Schedule 3 preparations should be re-scheduled to Schedule 4, or whether any re-scheduling to Schedule 4 should only apply to combination analgesic products containing codeine.
- Consideration may be given as to whether the Schedule 2 entry for codeine should also be amended.

The above amendments were proposed in response to public applications received by the delegate for medicines scheduling to up-schedule products containing codeine to become prescription-only medicines (Schedule 4).

As outlined in the Regulations, this pre-meeting notice specified that these proposed amendments would be referred for scheduling advice to the ACMS at the July 2015 meeting. The ACMS comprises independent experts as well as state and territory representatives who provide advice to the medicines scheduling delegate.

The pre-meeting consultation period was open for public comment for 20 business days and closed on 7 May 2015. During this time the TGA received 60 pre-meeting public submissions for codeine. Of these, 29 submissions supported the proposal to up-schedule codeine products to Schedule 4. There were 25 submissions that opposed the proposal. Six (6) submissions did not state whether or not they supported the proposal. All of the pre-meeting public submissions were considered by the ACMS at the 'July 2015' meeting (which was held in early August 2015). Also considered was the advice of an independent pain specialist who was contracted to evaluate the re-scheduling proposal. The expert supported the proposal to up-schedule Schedule 2 and Schedule 3 codeine products to Schedule 4. The ACMS advice to the delegate was to delete the current Schedule 2 and 3 entries for codeine and amend the current Schedule 4 and 8 entries to reflect this change.

Interim decision public consultation

On 1 October 2015, under subsection 42ZCZP/42ZCZQ of the Regulations, the TGA website published the delegate's interim decision and the reasons for the decision. Further submissions were also invited from the applicants and parties who made valid pre-meeting submissions. The delegate's interim decision was to delete the current Schedule 2 and 3 entries for codeine and amend the current Schedule 4 and 8 entries to reflect this change. The reasons for this interim decision to up-schedule are provided in the published [delegate's interim decision](#) and outlined in the section titled '*What is the problem?*' (p. 13).

The invitation to make submissions was open for 10 business days and closed on 15 October 2015. During this interim decision consultation period the TGA received 127 public submissions. Of these, 14 supported the decision and 113 opposed the decision. The reasons were similar to the pre-meeting submissions. It was noted that comments made during the interim decision consultation period would be taken into consideration in any final decision on any implementation date.

Additional consultation period

In order to give due consideration to the submissions received in the interim decision public consultation period and to seek further advice from the ACMS at its March 2016 meeting, the medicines scheduling delegate on 18 November 2015 deferred a [final decision](#) on the proposed codeine re-scheduling.

The TGA then sought further advice and public comment on several options for codeine re-scheduling via an [additional consultation period](#) that was open from 10 December 2015 through 29 January 2016. The scheduling options included:

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.

The medicines scheduling delegate outlined a provision of the re-scheduling options listed above, that they were not precluded from considering alternative scheduling options.

The TGA received 49 public submissions from this additional consultation. Roughly equal numbers of submissions were received either for or against the interim decision. Many submissions were copies of previous submissions.

Summary of public submissions

Public submissions received by TGA in response to all three consultations were from the following groups of stakeholders: consumers, industry, peak bodies, healthcare professionals, and state and territory government bodies.

The following section outlines the main points from all public submissions and stakeholder categories. These have been separated into submissions either supporting or opposing the up-scheduling.

Public submissions supporting up-scheduling

Of the 60 pre-meeting public submissions for codeine, 29 supported the proposal to up-schedule codeine products to Schedule 4. Of the 127 public submission received following the interim decision, 14 supported the decision. Of the 49 public submissions received from the additional consultation in December 2015, roughly half of the submissions supported the interim decision. When comments were made regarding improved labelling, all submissions supported this measure. The majority of comments regarding reducing pack size were also supportive.

Consumers

Consumers who supported up-scheduling often referred to relatives or friends who were addicted to codeine and that codeine was too easy to access and contributed to illnesses. There were numerous personal accounts of dependence, addiction and side effects, increasing over the past 10 years. It was suggested by some consumers that up-scheduling would reduce the potential for abuse, and that preventing easy access to an opioid would require patients to seek other low risk medications or get further medical advice. In addition, they felt that up-scheduling would reduce the potential for harm, particularly from complications due to overdose in codeine products combined with paracetamol or ibuprofen. Some felt that it was not currently possible for pharmacists to monitor and control safe use of low-dose codeine. Some consumers felt that real time monitoring would not be effective, would be costly and clumsy, and could involve risks to pharmacy staff who refuse to supply codeine.

Industry

Most members of the pharmaceutical industry were opposed to up-scheduling codeine to a prescription-only medicine. An exception was one sponsor who did not manufacture a codeine-containing product. This company supported up-scheduling.

Healthcare professionals and related peak bodies

Most healthcare professionals – including GPs, pain specialists, addiction specialists, psychiatrists, anaesthetists, hospital pharmacists, and their relevant representative medical colleges and societies – supported up-scheduling codeine to a prescription-only medicine. This was due to numerous studies and clinical evidence showing misuse and abuse related to codeine posed a significant risk to public health. If ease of access to an opioid was restricted, patients would seek other low risk medications and/or further medical advice. They stated that codeine-related patient numbers were increasing, with intensive and long-term treatment management being required. Further discussion points provided by healthcare professionals and related peak bodies included the inter-individual variation to codeine metabolism causing increased risks, and the known toxic side-effects routinely observed in hospitals. There was evidence of substantial risks to addiction and toxicity associated with ibuprofen or paracetamol in combination products. Many agreed that OTC codeine combination products do not meet the standards required to achieve acceptable safety and efficacy. Some stated that codeine doses are sub-therapeutic in OTC codeine combination products, and there was a lack of data to support its efficacy as an effective analgesic or cough suppressant.

Public submissions opposing up-scheduling

Of the 60 pre-meeting public submissions for codeine, 25 opposed the proposal to up-schedule codeine products to Schedule 4. Of the 127 public submission received following the interim decision, 113 opposed the decision. Of the 49 public submissions received from the additional consultation in December 2015, roughly half of the submissions opposed the interim decision.

Consumers

Over 70% of consumers raised the potential of additional financial burden to both patients and Medicare from the costs of increased GP visits if codeine were to only be available by prescription. Other common points raised by roughly 25% of consumers were that combination low-dose opioid pain relief was believed to be more effective than non-opioid alternatives, that they were able to self-manage their own pain relief, that up-scheduling would prevent them from accessing adequate pain relief, and that RTM and education would provide better regulation than up-scheduling. There were also a few concerns that people in rural areas may not be able to quickly access a GP if codeine becomes prescription-only.

Industry and related peak bodies

Most pharmaceutical companies opposed the up-scheduling, as did the Pharmacy Guild of Australia, the Pharmaceutical Society of Australia, Australian Self-Medicating Industry, and some other consumer groups. Most discussed that a reduction in pack size and mandatory warning statements regarding the potential for dependence would be more acceptable. They also believed that pharmacists are able to discuss alternative treatments and manage risks with codeine, or that a national, RTM system is preferred. Some thought that there was insufficient evidence that the morbidity issues result from cold and flu preparations.

Healthcare professionals

Some healthcare professionals suggested that re-scheduling may result in under-treatment and over-investigation, and that re-scheduling may cause at-risk patients to turn to alternative drugs for pain relief, such as alcohol, cannabis, psychostimulants; these alternatives were reasoned to have other risks. They also pointed to research suggesting that codeine is effective for acute pain, thus meeting the claim of short term relief.

General practitioner considerations

To better understand the issues and implications of codeine re-scheduling for Australian general practitioners (GP) and general medical practices, a meeting was conducted with the Australian Medical Association (AMA).

The expected increase in the number of patients presenting to GP practices requesting a script for codeine as a result of the re-scheduling of codeine-containing products to Schedule 4 was welcomed by GPs. Firstly, the initial increase in previously self-managed chronic pain sufferers presenting to their GP will result in better diagnosis and condition management by GPs. For example, headaches are often misdiagnosed by patients as migraines and subsequently mistakenly self-treated with analgesics. However headaches may be a symptom of more complex issues originating from the eyes, neck and/or back and may even be a result in changes in blood pressure. These types of conditions can be identified and treated more effectively by a GP through appropriate pharmacological options, and in some cases more effective alternative non-pharmacological options such as physiotherapy, osteopathy and/or exercise. Secondly, previously undiagnosed and unaccounted for dependent users, unaware of their codeine dependency or too embarrassed to seek help, will have to see a GP to obtain codeine and therefore receive the help they need to overcome their addiction. The behaviour of chronic pain sufferers and codeine dependent users are expected to drastically change as a result of GP consultation.

Many GPs are well-informed regarding the risk versus benefit of codeine-containing drugs and are able to restrict the potential for overdose or daily abuse by limiting the number of daily tablets dispensed or the number of script repeats. This promotes ongoing GP management to ensure that the course of treatment is still appropriate or to ascertain any health complications regarding the drug. It was proposed however, that some GPs, without awareness of the regulatory change, will prescribe high dose codeine-containing products in order to reduce the dose of paracetamol ingested by the patient, without undertaking a full assessment or further investigation into the cause of the patient's pain. This will have to be managed through an appropriate GP education program.

Primary Health Networks are currently developing pathways and decision assistance tools for chronic pain condition management. These tools will enable GPs to better diagnose and manage chronic pain and if necessary, refer patients to pain management clinics. However, this is where the bottleneck currently lies with current access to these facilities involving long waiting periods. The model of pain clinics will have to change to accommodate the re-scheduling of codeine-containing products to involve more outreach programs and communication with GPs.

In addition to issues with pain management clinic infrastructure, another concern from a GP perspective is the lack of suitable alternatives to OTC codeine-containing analgesics for the over-65 population. Non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen), a commonly used alternative to codeine-containing products, are not recommended for use in patients over the age of 65 due to the increased risks of cardiovascular disease, renal impairment and the increased risk of gastrointestinal ulcers.

Targeted consultations with industry and peak bodies

To help support the final decision relating to the re-scheduling of codeine, this RIS is modelling the economic, social and regulatory impacts of the codeine scheduling options. KPMG were contracted to undertake the economic modelling and financial quantification of the regulatory impact of the proposed changes to codeine scheduling. The development of the regulatory cost estimates was informed by targeted consultations with sponsors who currently produce codeine-based products in the OTC market. The target sponsors were Sandoz Pty Ltd, Sanofi-Aventis Australia Pty Ltd, GlaxoSmithKline Consumer Healthcare Pty Ltd, Soul Pattinson Manufacturing Pty Ltd and Johnson & Johnson Pacific. These companies occupy both distinct and overlapping segments of the OTC and prescription market and were able to provide a range of perspectives given the different incentives and risks that are intrinsic to their business models.

In preparation for these interviews, all sponsors were provided with background material and a list of questions for discussion (Appendix A). The interviews were structured around product strategy, market response, labelling, packaging, updated listing and regulatory approvals, and implementation. Industry input contributed to the development of the regulatory costing model, allowed for the testing of baseline assumptions and gave some insight into anticipated supply and demand behaviour of market participants in response to the re-scheduling options.

Interviews with industry

Five pharmaceutical companies that currently sponsor codeine-containing products on the Australian Register of Therapeutic Goods (ARTG) were interviewed:

- GlaxoSmithKline Consumer Healthcare Pty Ltd - a major provider of Schedule 2 and Schedule 3 medicines containing codeine.
- Johnson & Johnson Pacific - a major provider of Schedule 2 and Schedule 3 medicines containing codeine.
- Sandoz Pty Ltd - a major provider of Schedule 2 and Schedule 3 (OTC) medicines containing codeine.
- Sanofi-Aventis Australia Pty Ltd - a major provider of Schedule 3 (OTC) and Schedule 4 (prescription only) medicines containing codeine.
- Soul Pattinson Manufacturing Pty Ltd - a major provider of Schedule 2 and Schedule 3 medicines containing codeine.

In preparation for these interviews, all sponsors were provided with background material and a list of questions for discussion (Appendix A). Industry input contributed to the development of the regulatory costing model, allowed for the testing of baseline assumptions and gave some insight into anticipated supply and demand behaviour of market participants in response to the re-scheduling options.

Interviews with peak bodies

Further interviews were conducted with representatives from peak bodies to inform the development of the economic and social model:

- Australian Medical Association (AMA) - as the peak body representing registered medical practitioners and medical students of Australia;
- Pharmaceutical Society of Australia (PSA) - as the peak body representing pharmacists in Australia;
- Australian Self Medication Industry (ASMI) - as the peak body representing companies involved in the manufacture and distribution of consumer healthcare products in Australia; and
- Pharmacy Guild of Australia (PGA) - as the peak body representing pharmacists and pharmacies in Australia.

A high level summary of industry responses (including peak bodies) are provided here without direct attribution to specific stakeholders. This is intended to provide an overall picture of the feedback and the key themes that emerged from the meetings and in which informed the modelling.

Topic 1 - Product strategy

Sponsors were asked about how they would respond to up-scheduling decisions and what factors would be considered in determining their product strategy. There was a high level of concern by Schedule 2 and Schedule 3 sponsors about the impact of up-scheduling on their business. Sponsors identified a number of issues that undermined the commercial viability of up-scheduled codeine products. These issues were fundamentally connected to the different distribution and market access models associated with Schedule 3 and Schedule 4 arrangements, and uncertainty about the level of demand for lower dosage codeine products given the current prescribing habits of GPs.

Key points were:

- Schedule 2 sponsors are unlikely to migrate these products to Schedule 4. It is likely that most Schedule 2 sponsors will migrate Schedule 2 products to Schedule 3, and would rationalise their product portfolio with generic brands.
- Schedule 3 sponsors would evaluate the commercial viability of moving these products to Schedule 4; however, this would be largely contingent on their expectations about demand and confidence that GPs would change their prescribing habits to account for different dosage options.
- Sponsors with branded products highlighted concerns about the impact of discontinuing products on brand equity and the regulatory barriers to redeploying or reformulating well known and trusted brands which are a source of value for these companies.

Topic 2 - Market response

Sponsors were asked to provide views on what impact the different options would have on the behavior of customers (across different segments) and the level of demand and substitution they would expect to see in the market.

Key themes were as follows:

- The introduction of warning labels and reduced pack sizes would slightly reduce overall revenue; however the overall demand for codeine would largely remain.
- The up-scheduling of codeine from Schedule 2 to Schedule 3 would reduce demand but there would still be a market for codeine-based cough and cold products. However, consumers would be presented with less range and choice as products move behind the counter. This would necessitate some degree of product rationalization.
- The up-scheduling of codeine from Schedule 2 to Schedule 4 would effectively see these product lines discontinued.
- The up-scheduling of codeine from Schedule 3 to Schedule 4 would reduce overall demand for medium dosage codeine products, however a sizable segment of these existing customers would continue to seek out codeine products and visit a GP to obtain a prescription. Sponsors all considered it likely that these consumers would visit their GP and receive access to higher dosage products with larger pack sizes which could lead to perverse outcomes.
- The Schedule 3 market is essentially entirely made up of consumers. Hospitals and other institutions do not bulk purchase OTC codeine products (tending to use paracetamol or move to higher strength opioids).

Topic 3 – Reduced pack size

Sponsors were asked to comment on whether they have products or manufacturing arrangements that would readily accommodate the requirements of a 3-day pack (both in terms of the outer pack and the inner blister packs). There was a mixed response regarding this question, with about half of the sponsors indicating they already produced a 3-day pack or had production lines that could be used to do so, and thus they could accommodate this at essentially no cost. Others would incur costs for re-tooling machinery to modify the depth of the outer pack or the length of the inner blister pack.

The sponsors interviewed stated that costs appeared to depend on whether the manufacturing was done in Australia or overseas. Re-tooling in Australia is more expensive (and potentially cost prohibitive) and ranges from between \$30,000 to \$150,000. Re-tooling overseas is cheaper and ranges from between \$10,000 to \$30,000. The sponsors also expressed an opinion that implementation in local facilities could be executed more quickly (6 months) whilst changes to overseas facilities would take longer (12 months).

Topic 4 – New warning labels

Sponsors were asked to describe the steps involved in adding new labels, and the costs associated with these steps. Broadly, the steps identified were the development of artwork and design, internal review, quality assurance and implementation. The range of costs provided by sponsors was between \$2,000 and \$6,500.

Sponsors noted they would look for opportunities to roll out label updates into others which were already in the pipeline. Updates would typically occur once every 3 years.

Implementation timeframes are between 6 and 12 months. Similar to packaging, overseas production arrangements required longer lead-times as there is less flexibility in scheduling updates into manufacturing change windows.

Topic 5 – Updated listings

Sponsors were asked to comment on time or cost of regulatory forms and other compliance processes connected to the various options. Key points were:

- C1/C2 forms¹³² were noted as relatively straight forward. With sponsors indicating time required to complete, undertake internal review and submit forms being between 4 – 10 hours of effort.
- Sponsors indicated updating Product Information (PI)/Consumer Medicines Information (CMI) documents would also be straightforward. In the event a new PI/CMI had to be created (such as Schedule 2 up-scheduling to Schedule 3) sponsors would not seek to create one from scratch but leverage a model PI already being used in that schedule.
- Sponsors did not anticipate up-scheduling to Schedule 4 (if they were currently in Schedule 2 or Schedule 3) would cause any difficulties with respect to GMP conformity. The sponsors consulted were all confident their facilities were GMP compliant and also noted those facilities were already manufacturing other Schedule 4 products.
- In their responses, sponsors indicated that based on precedent, they would expect the TGA to upgrade Schedule 2 and Schedule 3 products into Schedule 4. They cited the standard registration process for a prescription medicine as material cost and time delay that could require up to 24 months subject to the scope of the application requirements.

Topic 6 – Implementation timeframes

Implementation timeframes were discussed with sponsors throughout each of the topics to understand the minimum and ideal timeframes connected with different change processes. The purpose of this topic was to understand any other implementation considerations pertinent to industry.

Several sponsors expressed concerns about the lack of certainty concerning the implementation timeline and arrangements that would accompany a decision to up-schedule. They noted the critical importance of implementation timeframes in enabling business to reposition themselves in the event of an adverse outcome. They also noted that a short implementation timeframe would potentially increase costs and make it difficult to reposition themselves in the market without significant losses in revenue. In this respect, sponsors emphasized the engagement of the TGA would be critical towards assisting their planning.

Broadly, sponsors indicated a reasonable end-to-end implementation timeframe would, at a minimum, be between 18 to 24 months. However, sponsors noted their concerns that an 18 to 24 month timeframe may be perceived as being at odds with the safety/risk rationale of the interim decision and that the TGA would be presented with a moral dilemma in balancing the two.

Other key themes were as follows:

- Pharmacies generally hold between 1 to 2 -month worth of stock depending on their location
- Most manufacturers do not hold large amounts of produced stock but make to order. However, they do make bulk purchases of components and materials and these can take between 4 and 9 months to turn over

¹³² For more information regarding change applications, see the TGA website at <https://www.tga.gov.au/book-page/step-2-determining-your-application-level-and-change-codes>

- Shelf life of codeine products is 24 months. Sponsors were concerned a short implementation timeframe may require some residual products to be recalled from shelves which would be a costly exercise and involve reverse logistics
- The minimum timeframes to comply with an up-scheduling decision appears to be around 9 months. However sponsors noted this assumes that there is no business case development or evaluation of commercial viability to up-schedule which they considered to be unreasonable. They further expressed a view that a longer timeframe is needed to enable this to be undertaken in an orderly way, and
- Sponsors indicated time is also needed for GPs to be educated about the changes (in the event of an up-scheduling) to ensure their prescribing habits adapt to the new situation, and that medium dosage codeine products (at 12.5mg) are prescribed when appropriate. Sponsors also sought clarity as to whether the government or industry would be expected to fund the costs of GP education.

Implementation timeframe

The implementation timeframe for any decision that impacts on labelling, pack size or scheduling has the potential to increase regulatory costs. The cost estimates outlined in the remainder of this section assume an implementation timeframe of 18 months. However, it is important to note that a change in timeframe would impact the estimated costs. For example, a shorter implementation timeframe may mean that sponsors cannot make the necessary changes in time (or obtain the necessary approvals), which, in an extreme case, could require products to be removed from the shelves, or may mean that revised products cannot come to market by the time existing products are withdrawn. A longer implementation timeframe may enable a greater proportion of compliance activities (such as a labelling update) to be rolled into other scheduled changes thereby reducing the compliance burden, while also enabling sponsors who are adversely impacted to reposition themselves to adjacent markets.

There are several categories of changes which are impacted by implementation timeframes:

- time to implement labelling changes (compliance).
- time to reduce pack sizes (compliance).
- TGA approval timeframes (approvals).
- stock recall (compliance).
- product strategy and portfolio diversification (business).

Figure 7 below illustrates indicative implementation timeframes for each of these categories.

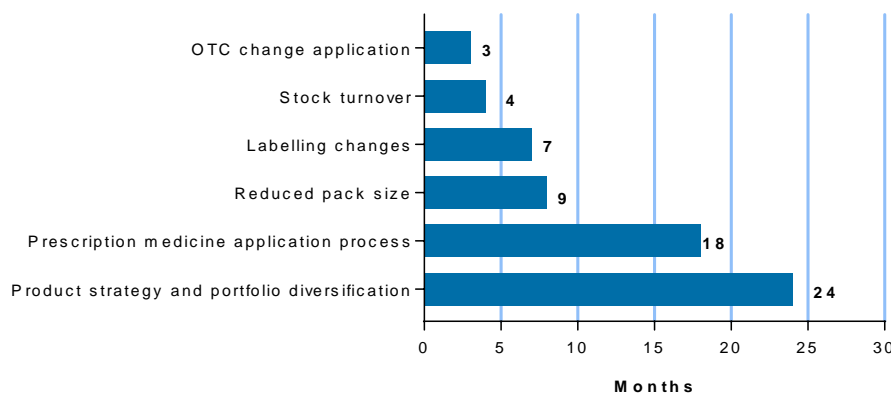


Figure 7: Implementation timeframe

Labelling changes

Consultation has identified that the implementation of labelling changes will take between 6-8 months. The component steps involve the development of artwork, internal approvals, regulatory approvals and implementation. This falls within the 18 month transition window provided by the TGA for recent RASML updates.¹³³

Stock turnover

Consultation with manufacturers has identified stock turnover timeframes of between 6 weeks and 4 months. Different parts of the supply chain will hold different levels of stock. Codeine based products have a shelf life of 24 months, although this is not anticipated to be a constraint, given the level of turnover.

Product strategy and diversification

In response to a decision, manufacturers and retailers who currently have a market share of codeine-based products will have a planning and investment timeline to reposition their product portfolio. Some sponsors may require registration of new ARTG entries that have a 12 month lead time. Following this, manufacturers may require up to an additional 6-12 months to assemble the production line and source materials. This will vary depending on whether production is local (increased flexibility), or overseas (less flexibility). An 18-month timeframe would be ideal to allow impacted manufacturers (and to a lesser degree sponsors) to reposition, and therefore maintain, their market share.

Reduce pack size

Manufacturers who do not have existing production lines that can accommodate a reduced outer pack, or inner blister pack, will need to make changes to their production line. Discussions with manufacturers have indicated this would take 9 months from procurement to implementation. In the event that this is not commercially viable, sponsors could seek an alternative manufacturing site. Although in the event that the alternative site does not have GMP certification this may be a lengthier process.

OTC C1/C2 level applications

The anticipated timeframes for approval of C1/C2 change applications are approximately three months.¹³⁴

Applications to register a prescription medicine (Schedule 4)

Any up-scheduling of Schedule 2 and Schedule 3 medicines to Schedule 4 would not require the registration of new prescription medicine, as codeine is not a new ('novel') chemical entity. In the case of Schedule 3 medicines up-scheduled to Schedule 4, the processes for minor variations to registered prescription medicines would be followed. This would entail the submission of a Category 3 application (with an associated processing timeframe of 45 working days). Specifically a '*9D(3) Category application to vary an ARTG entry*' would be used with the existing PI and CMI submitted with the application. For Schedule 2 medicines up-scheduled to Schedule

¹³³ www.tga.gov.au/publication/required-advisory-statements-medicine-labels-rasml

¹³⁴ See the TGA website for more information on change applications: <https://www.tga.gov.au/book-page/step-2-determining-your-application-level-and-change-codes>

4, a new PI and CMI would need to be produced (though these could leverage existing PIs and CMIs for medicines with codeine as an active ingredient). This would be considered a Category J variation ('Changes to product information requiring the evaluation of data'), with a maximum processing timeframe of 255 working days (Category 1 application). However, that as this application does not relate to a new chemical entity or a new indication(s) that the actual processing time (and associated data requirements) is likely to be considerable less than this. The standard process to register a new prescription medicine is estimated to take between 12 and 24 months. However, codeine is already an established active ingredient and is included in many OTC and prescription medicines already in the market.

The implementation timeframes for each option are summarised in Table 21. Outlined for each option are the associated constraints and the minimum time required for option implementation, in addition to industry preferred timeframes.

Table 21: Summary of implementation timeframes

	Minimum implementation timeframes	Desired timeframes by industry
Option 2 Add warning label and reduce pack size on Schedule 2 products	9 months Constraint: packaging changes (overseas)	12 months
Option 3 Up-schedule Schedule 2 to Schedule 3, and add warning label and reduce pack size	9 months Constraint: packaging changes (overseas)	12 to 18 months Driver: product strategy and repositioning
Option 4 Up-schedule Schedule 2 products to Schedule 4	12 months Constraint: regulatory approval	18-24 months Driver: product strategy and repositioning
Option 5 Add warning label and reduce pack size on Schedule 3 products	9 months Constraint: packaging changes	12 months
Option 6 Up-schedule Schedule 3 to Schedule 4	12 months Constraint: regulatory approval	18-24 months Driver: product strategy and repositioning

Source: KPMG report, Table A4

What is the preferred scenario?

Codeine is a commonly used drug of abuse, both internationally and in Australia. The presence of codeine in OTC combination analgesics and the development of codeine dependence contributes to severe adverse health outcomes associated with the overdose of other active constituents, such as paracetamol or ibuprofen. There is substantial evidence of harm from abuse or misuse of codeine-containing medicines, including deaths.

The medicines scheduling delegate of the Department of Health is considering several options to change the way codeine is made available in Australia by amending the Poisons Standard. Low-dose codeine is currently available OTC in pharmacies in cough and cold medicines (Schedule 2) and in combination with other analgesics (Schedule 3). High dose codeine and other opioids such as morphine and pethidine are either available only by prescription (Schedule 4) or are controlled drugs (Schedule 8). Several options have been considered, and are summarised in Table 1 (p. 36). These options are grouped into four scenarios in Table 2 (p. 36) representing the potential final scheduling decision.

Scenario 4, whereby all Schedule 2 and Schedule 3 codeine-containing medicines will be up-scheduled to Schedule 4, is the preferred option based on both public health considerations and net economic benefits, as discussed below.

Economic and regulatory costs or savings are not necessarily considered by the delegate under the [Scheduling Policy Framework \(SPF\)](#) and the scheduling regulatory framework as specified in Therapeutic Goods legislation. Scheduling decisions are made according to subsection 52D(2) of the [Therapeutic Goods Act 1989](#) (TG Act) taking into account the following matters of public health (where relevant) as set out under section 52E of the TG Act:

- (a) the risks and benefits of the use of a substance;
- (b) the purposes for which a substance is to be used and the extent of use of a substance;
- (c) the toxicity of a substance;
- (d) the dosage, formulation, labelling, packaging and presentation of a substance;
- (e) the potential for abuse of a substance;
- (f) any other matters that the Secretary considers necessary to protect public health.

In addition to considering the above matters prescribed above under subsection 52E of the TG Act, the scheduling delegate must also consider the [factors](#) in the SPF.

The specific reasons for the initial recommendation to up-schedule codeine included matters relevant under section 52(E) of the TG Act (see p. 28 '*Scheduling of medicines*') were outlined and discussed in detail earlier under the following headings:

- [Codeine as a prodrug and its metabolism](#);
- [Codeine toxicity and alternative products](#);
- [Codeine use, misuse and abuse](#);
- [Current scheduling inconsistencies](#); and
- [International scheduling considerations](#).

Additional public health matters relating to the health concerns of OTC codeine have been discussed under '[Morbidity and death](#)' and '[Dependence and addiction](#)'.

Furthermore, there is substantial published evidence for the involvement of codeine in cases of drug toxicity, contributing to both accidental and intentional deaths, many of which can be attributed to the misuse of combination codeine medicines. This, in combination with the limited data supporting the incremental effectiveness of codeine associated with codeine combination products, results in a negative risk/benefit analysis.

Due to harm from abuse or misuse of codeine, medicines containing codeine are tightly regulated in many countries. Regulatory controls include limits on pack sizes, label warnings on packaging, warnings in consumer information leaflets, and availability of codeine-containing medicines by prescription only. In Australia, similar regulatory controls are required to protect public health, and in addition, regulatory controls take into consideration restrictions to access. For example, the up-scheduling of codeine will remove codeine-containing medicines from general sale, and limit access. Under these circumstances, limits on pack sizes is not required and label warnings will be provided for by the patients' medical practitioner.

The identified health benefits of [Scenario 4](#), which involves up-scheduling all OTC codeine products to Schedule 4, include:

- accidental death prevention
- improved quality of life, resulting from the exploration of alternative, more effective treatment options that would not have previously been explored
- prevention of adverse events related to unintentional overdose of paracetamol or ibuprofen, and
- reduced dependence and reduced risk of dependency.

When considering both the scheduling factors in the SPF as well as the matters listed in the TG Act, it is clear that codeine meets the criteria for [Schedule 4](#) (or higher). Therefore the up-scheduling of codeine to Schedule 4 is the preferred option based on the substantial gains in the protection of public health and safety.

This RIS has been completed to better understand the regulatory, social and health impacts of any change to the scheduling of codeine, including the risk to consumer safety if no action is taken.

The regulatory cost estimates and health economics have been informed by feedback from individual consumers, healthcare professionals and the pharmaceutical industry, as well as state and territory jurisdictions. Targeted consultations were held with key stakeholders, including sponsors who currently produce codeine-based products in the OTC market, to document the potential business process impacts and any implementation timeframes to comply with any change in codeine scheduling. These consultations were aimed to minimise the regulatory impact and to address identified issues.

The regulatory and economic costs and benefits are summarised in Table 20. When the regulatory costs, health economic costs, and health economic benefits are all considered, a net benefit to society is only found for Scenario 4 (Options 4 and 6). Scenario 4 yields a net benefit of \$5,206.72 million for the ten years from 2017-2026, whereas Scenarios 2 and 3 result in a net cost to society. The economic benefits are driven by gains in quality of life, deaths prevented and a net reduction in out-of-pocket costs to the consumer.

The positive net benefit for Scenario 4 is robust to a wide range of sensitivity analyses. When the assumptions for costs are maximised and benefits are minimised, the net benefit remains positive. The net benefit was most sensitive to the average QALY gain resulting from additional treatment received for pain symptoms and the number of repeat scripts. The result was only moderately sensitive to the discount rate, number of deaths prevented, and the co-payment for GP and specialist consultations. The substantial health benefits are driven by the gain in QALY as

patients receive treatment they would otherwise not have accessed that leads to more effective therapy compared to low-dose codeine combination medicines.

Therefore the preferred scenario, Scenario 4, consisting of Options 6 and 4 (remove Schedule 2 and Schedule 3 entries and add a new Schedule 4 entry for codeine), will deliver significant protection to public health and safety as a result of positive changes in consumer purchasing behaviour, raise awareness of codeine dependency through education, and increase exploration of alternative more effective therapeutic and treatment pathways for pain management. Further, Scenario 4 provides a significant net economic benefit to society of \$5,206.72 million over a 10-year period from 2017-2026.

Appendix A

Interview questionnaire for sponsors

Context

On 1 October 2015, the Therapeutic Goods Administration (TGA) published an interim decision by the medicines scheduling delegate (the delegate) to adopt the proposal that all medicines containing codeine currently available over-the-counter (Schedule 2 and Schedule 3) be up-scheduled to Schedule 4, prescription only medicines. See the TGA website for further detail regarding this decision, including the reasons for the decision: [Interim Decision, October 2015](#)

The TGA undertook a series of public consultations regarding the interim decision, as well as seeking comment on alternative courses of action. Subsequently, on 19 November 2015, the delegate announced that a final decision on the re-scheduling of codeine would be deferred to allow a more thorough consideration of the numerous submissions and broader implications to current products in the market. See the TGA website for more information regarding this decision: [Final Decision, November 2015](#).

The TGA will be undertaking a regulatory impact review and producing a Regulation Impact Statement (RIS). To assist with production of the RIS, on 2 August 2016, TGA engaged KPMG to undertake economic, social and regulatory impact modelling on the range of codeine scheduling options as developed through the public submission process. The KPMG modelling will be provided to the TGA in late August 2016 to support the development of the RIS.

KPMG is engaging with codeine sponsors to better understand the potential impacts on industry, understand potential implementation considerations, and inform the development of modelling to support the development of a RIS.

Scenarios

Formally, the options being considered for the purposes of constructing the RIS are presented in a step-wise manner, as follows:

Option 1	No change - the current scheduling of codeine remains appropriate.
Option 2	The current Schedule 2 entry for codeine in cough and cold medicine preparations be amended to reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction.
Option 3	The current Schedule 2 entries for codeine in cough and cold medicine preparations be up-scheduled to Schedule 3, and that the pack size be reduced to not more than 3 days' supply, and include a label warning that codeine can cause addiction.
Option 4	To up-schedule the current Schedule 2 entries for codeine to Schedule 4 and amend the current Schedule 4 and 8 entries.
Option 5	The current Schedule 3 entries for codeine (including, but not limited to codeine-containing analgesics) be amended to reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause

	addiction.
Option 6	To up-schedule the current Schedule 3 entries for codeine to Schedule 4 and amend the current Schedule 4 and 8 entries.

In practice, these options could result in the following scenarios:

Scenario 1 (Option 1)	No change to the status quo.
Scenario 2 (Options 2 and 5)	<p>Schedule 2 (S2) and Schedule 3 (S3) entries for codeine (including, but not limited to, cough and cold medicine preparations and codeine-containing analgesics) be amended to reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction.</p> <p>Summary</p> <ul style="list-style-type: none"> – Reduce pack size and include warning label for S2 and S3
Scenario 3 (Options 3 and 5)	<p>The current Schedule 2 entries for codeine in cough and cold medicine preparations be up-scheduled to Schedule 3, and then all Schedule 3 entries (i.e. those currently Schedule 2 and those previously Schedule 2) for codeine (including, but not limited to, cough and cold medicine preparations and codeine-containing analgesics), be amended to reduce the pack size to not more than 3 days' supply, and include a label warning that codeine can cause addiction.</p> <p>Summary</p> <ul style="list-style-type: none"> – S2 up-scheduled to S3 – Reduce pack size and include warning label for S3
Scenario 4 (Options 4 and 6)	<p>Schedule 2 and Schedule 3 entries for codeine (including, but not limited to, cough and cold medicine preparations and codeine-containing analgesics) be up-scheduled to Schedule 4 (S4).</p> <p>Summary</p> <ul style="list-style-type: none"> – S2 and S3 up-scheduled to S4

Topic 1 – Product strategy

1. How would your product strategy respond to an up-scheduling decision (i.e. Scenarios 3 or 4)?
 - 1.1. Would you rationalise your codeine portfolio?
 - 1.2. Would the current S2 and S3 product lines be reformulated?
 - 1.3. Would you substitute this share of the market with non-codeine-containing S2 and S3 products and / or increased production of S4 product lines?

Topic 2 – Market response

2. (Contextual) How is the market for your S2 and S3 codeine products composed; i.e. principally individual patients or does this also include bulk institutional customers?
3. What are the anticipated impacts on demand for your products in the following scheduling scenarios? Consider impacts to individual patients (including different types of patients, i.e. acute / chronic users, dependent / non-dependent etc.), prescribers, institutional customers, and any other relevant demand groups.
 - 3.1 Scenario 3 (S2 up-scheduled to S3)
 - 3.2 Scenario 4 (for S2 up-scheduled to S4)
 - 3.3 Scenario 4 (for S3 up-scheduled to S4)
4. In the case of a re-scheduling decision (i.e. Scenarios 3 and 4), what segment of patients currently consuming your codeine-containing S2 and S3 product lines do you anticipate will substitute these for other, non-codeine-containing S2 and S3 products (rather than seek a prescription for the S4 products?)
5. Are there any other market responses that you are anticipating?

Topic 3 – Reduced pack sizes

6. (Contextual) How are changes to your packaging (outer and inner) implemented for your products?
7. In terms of physical pack sizes, what would be required to conform with a decision regarding limiting pack sizes to no more than three days' supply?
 - 7.1 Does this differ for types of packaging for all codeine-containing products, i.e. blister pack inserts and boxes, liquid preparations, tablet bottles etc.?
 - 7.2 Do you have product lines currently in production that would meet the reduced pack size requirements, i.e. through placing a reduced number of blister pack inserts in existing boxes?
 - 7.3 What upfront costs would be incurred to implement changes in outer or blister packs per ARTG listing? (Either in dollar terms or FTE resources.)
8. What are the timeframe involved in making these changes?

Topic 4 – New warning labels

9. (Contextual) How are changes to labelling (outer and, where required, inner) implemented for your products?
10. What would be required to conform with a decision regarding mandatory warning labels?

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Scheduling & Committee Governance Section/ Regulatory Education and Planning Branch	14/11/2016
V 1.1	OBPR reviewed publication	Scheduling & Committee Governance Section/ Regulatory Education and Planning Branch	29/11/2016

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia

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

<https://www.tga.gov.au>

Reference/Publication #