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The Secretary
Scheduling Secretariat
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Dear Sir or Madam,

Notice of delegate's interim decisions under subsection 42ZCZP the Therapeutic Goods Regulations 1990 and invitation for further submissions, in relation to the ACMS Meeting of July 2015

We refer to the notice inviting further submissions and would like to provide comment in relation to the interim decision regarding codeine scheduling from the July 2015 meeting of the ACMS.

ASMI (Australian Self Medication Industry) is the peak body representing companies involved in the manufacture and distribution of consumer health care products (non-prescription medicines) in Australia. ASMI also represents related businesses providing support services to manufacturers, including advertising, public relations, legal, statistical and regulatory consultants.

ASMI appreciates the opportunity to provide further comment and we wish to address relevant matters under section 52E of the *Therapeutic Goods Act* 1989.

ASMI re-iterates the arguments put forward in our submission of 14 May 2015 and we seek to add the following comments in relation to the interim decision:

Overview

ASMI is opposed to the interim decision and our position can be summarised as follows:

- Limiting access to medicines for self-management of acute pain will create a significant burden on the healthcare system
    - While misuse and addiction are serious problems, the great majority of consumers use codeine containing analgesics appropriately.
    - For this great majority, the decision will make these products more expensive and more difficult to obtain.
    - There has been no evidence of misuse of codeine containing cold and flu products and applying the same restrictions to these products as to the codeine containing analgesics does not make sense because it is an inappropriate use of regulation and does not represent an appropriate risk-based decision. The current scheduling of codeine containing cold and flu products remains appropriate and there should be no change to the scheduling of these products.
    - The availability of a range of pain management options that are readily accessible without the need for a prescription addresses an important medical need.
    - The decision to up-schedule codeine containing analgesics will make short term self-management of acute pain more difficult and create a significant additional burden on the healthcare system and already overstretched GP resources.

- Restriction of codeine to prescription only will not mitigate the risk of misuse or abuse
    - Making all codeine containing products prescription only will not address the concerns of misuse and abuse, it will simply transfer it to already overstretched GPs and emergency departments of hospitals.
    - Prescription only scheduling is no guarantee against misuse or abuse and there are no mechanisms in place for prescription monitoring.
    - Evidence suggests that there are more people misusing prescription strength codeine containing analgesics than non-prescription codeine containing analgesics.
    - Reviews in other jurisdictions including the UK and New Zealand, with an equivalent medicines classification system and standard of healthcare to Australia, have maintained codeine containing product availability from pharmacies without evidence of an increased risk to public health.

- Pharmacists are accessible and suitably qualified to implement an effective risk mitigation strategy to address concerns of misuse or abuse
    - Pharmacists can ensure the right choice of medication for individual patients with appropriate referral to a medical practitioner if self-management will not deliver the best health outcome.
    - Identification of repeat purchasers enables those patients to be counselled on potential addiction risks and ensure referral to a medical practitioner.

- Real time monitoring is an effective risk mitigation approach to identify misuse and abuse
    - ASMI believes that a real-time-monitoring system should be put in place nationally as part of a package of measures including mandatory front-of-pack warnings and information resources for pharmacists and consumers.
    - ASMI has been working with pharmacy organisations and consumer organisations to develop a prototype monitoring system using experience gained from Project STOP.
    - There are no comparable mechanisms in place for prescription monitoring that provide the same level of risk oversight to mitigate potential risks

- The appropriateness of the existing Scheduling Policy Framework is a priority area for regulatory reform as part of the recent government Medicines Review
    - This decision represents unnecessary over-regulation and will result in a huge increase in costs for both consumers and government.
    - The current regulatory framework for scheduling is not fit for purpose as it does not facilitate a holistic assessment of the spectrum of public health consequences considering removal of a large proportion of OTC analgesics will leave a significant unmet medical need and demand from patients for accessible pain relief

- The proposed implementation date of 1 June 2016 is unrealistic
    - With respect to maintaining the compliance of existing products, the proposed implementation date of 1 June 2016 is completely unrealistic and ignores the practicalities associated with therapeutic goods supply chains (especially for seasonal products and those products sourced overseas).
    - With respect to developing and supplying replacement products, this timeframe is even more unrealistic. There has been no consideration of expedited regulatory pathways to facilitate the approval of alternative formulations or presentations. Such expedited pathways will be essential to maintain appropriate supply and ensure a viable medicines industry in Australia so as to provide a range of appropriate medicines to meet consumer needs.

Recommendations

Considering the magnitude of the impact of the decision (see below) a deferral in making a final decision is urgently required to ensure a full and transparent process is implemented.

ASMI calls on the Delegate to re-examine the decision to apply the same scheduling changes to codeine containing cold and flu products as to codeine containing analgesics. The current scheduling of codeine containing cold and flu products remains appropriate and there should be no change to the scheduling of these products.

ASMI calls on the Delegate to defer making a final decision in relation to codeine containing analgesics until:

1. A real-time monitoring system has been put in place and sufficient data collected,
2. A comprehensive examination of the impacts of the decision in the form of a Regulation Impact Statement (RIS) has been conducted, and,
3. The acknowledged shortcomings of the current Scheduling Policy Framework have been addressed.

Concerns about the Process

ASMI is concerned that the process by which the interim decision was reached has not been transparent and has not allowed interested stakeholders to examine all the relevant materials and provide comment in relation to them.

In particular, the scheduling proposal(s) which triggered the review have not been made public and neither has the evaluation report on which the delegate bases the interim decision.

Given the substantial impacts of this decision (see below), all affected stakeholders ought to have the right to examine the relevant materials in detail and provide responses to those materials.

The interim decision has a disproportionate focus on risk, with an inadequate examination of the benefits to consumers of timely access to a range of efficacious products.

Limitations of the Current Scheduling Policy Framework

The current scheduling policy framework governs the methodology for reaching a decision on scheduling. The factors to be considered are focused on risk and any consideration of broader public health implications that contribute to the benefit-risk balance is excluded from the process. For example the policy indicates that the following questions should be answered to ensure that the risk is understood as completely as possible:

- What is the hazard?
- How widespread is the hazard?
- In what circumstances will the hazard arise?
- What is the likelihood of the hazard occurring?
- Who or what is at risk?
- What are the consequences of the hazard in terms of severity (morbidity and mortality) and duration?

As part of the Review of Medicines and Medical Devices Regulation, the expert panel recommendations identified that the current scheduling framework is not fit for purpose and a recent workshop in Brisbane indicated broad agreement from stakeholders that the current governance requirements were outdated and not aligned with other jurisdictions. In particular a lack of transparency and a lack of balanced consideration of benefit are absent from the current process.

Real-time Monitoring System

ASMI believes that a real-time-monitoring system should be put in place nationally for S3 codeine containing analgesics and we have been working with pharmacy organisations and consumer organisations to develop a prototype system, which we are happy to demonstrate to interested parties.

ASMI notes that no corresponding system exists for prescription analgesics and that if the S3 codeine containing analgesics are up-scheduled then work on the prototype system will likely cease.

Up-scheduling will therefore remove any possibility of a monitoring system being put in place for these products.

Potential impact

There are close to 220[1] codeine containing analgesics on the ARTG. While we are unable to separate the prescription and non-prescription products, we are able to estimate that the non-prescription codeine containing analgesic products have approx. $135 million total annual sales in Australia.

There are close to 100 codeine containing cold and flu products on the ARTG and we estimate that these products have approx. $82 million total annual sales in Australia.

Should the S3 codeine containing analgesics be up-scheduled, the following is likely to occur:

- Consumers previously able to self-medicate will seek prescriptions from doctors for the lower dose products.
- Doctors may then prescribe the higher strength products already available on prescription (which are PBS reimbursed).
- There will be an increase in costs to the healthcare system.
- There will be an increased burden on GPs and emergency department of hospitals as consumers seek access to free consultations.
- There will be increased costs for consumers (for visits to their GP).
- There will be delays for consumers in accessing effective products (with associated losses in productivity).
- The lower dose products will likely be discontinued.
- Costs may prevent consumers accessing effective products leading to poorer pain management outcomes.

Also, there may be other, unanticipated impacts associated with a narrowing of OTC pain relief options.

Should codeine containing cold and flu products be up-scheduled, then there will be an increase in patients with minor, self-limiting conditions inappropriately presenting at GP clinics and emergency departments. Not only will this add delays and increase costs, but also has the potential to lead to increased antibiotic use.

Because of the likely far-reaching consequences of this interim decision for all stakeholders, we are calling for a full and transparent examination of all the regulatory and financial impacts of this decision. This detailed examination must be concluded before any steps are taken towards finalisation or implementation of the interim decision.

With this in mind, ASMI has sought advice from the Office of Best Practice Regulation (OBPR) in relation to the conduct of a Regulation Impact Statement (RIS) so that a comprehensive and objective review of the full impact can be undertaken.

[1] A search of the ARTG conducted on 14/10/2015 revealed 313 codeine containing products of which 96 had the word "cold" in the product name (with 217 products thereby assumed to be analgesics). No further separation of prescription and non-prescription products was possible.

Financial Impact

A Macquarie University study conducted on behalf of ASMI found that if S3 analgesics were up-scheduled to Prescription Only the cost to the economy would be substantial. Faced with the scenario of their S3 analgesics no longer being available over-the-counter at their local pharmacy, the research indicated that consumers would go to their doctor to continue to access their preferred medication. Only a quarter of respondents said they would use another OTC alternative. Over-the-counter analgesics containing codeine make up 22 per cent of the volume of analgesics sold in pharmacies and the decision to up-schedule will increase healthcare costs by at least $675 million annually. It is estimated the direct cost to Medicare for additional doctor's visits would be $170 million per annum and consumers would pay an additional $70 million each year. The indirect costs of lost productivity and delayed treatment are over $400 million[2].

New figures[3] reveal that up-scheduling codeine-containing cold and flu medicines would cost the Australian economy $257 million annually. With costs borne by government due to increased doctor visits, Medicare and dispensing costs at $53 million and a further $174 million due to productivity losses caused by the restricted access. The balance of costs would be borne by consumers.

Cold and Flu Products

ASMI calls on the Delegate to re-examine the decision to apply the same scheduling changes to codeine containing cold and flu products as to codeine containing analgesics.

There has been no evidence put forward of actual or potential misuse of the cold and flu products and so the decision to reschedule from S2 to S4 cannot have been made with a proper regard to section 52E of the *Therapeutic Goods Act*.

The Delegate has not provided any detail on whether there was a separate consideration of cold and flu products. It appears as though regulatory change has been based on an assumption of what *might* happen (i.e. that consumers who misuse codeine containing analgesics will also misuse codeine containing cold and flu products). This assumption is false and is contrary to evidence provided to the ACMS (and the Delegate) showing that there has been no increase in sales year-by-year suggestive of misuse. Cold and flu products have different labelling, different indications and multiple ingredients – which collectively mitigate the risk of misuse. These products should not be conflated with codeine containing analgesics. There is no specific evidence to justify up-scheduling and a scheduling decision should not be made without considering the different labelling, different indications and presence of other ingredients such as decongestants.

Furthermore, ASMI understands that while codeine containing cold and flu products have previously been referred to as codeine containing *cough* and cold products, in fact "cough" is not a TGA approved indication for these codeine containing products. The Delegate's assessment of these products therefore proceeds on the assumption that evidence relating to the efficacy of codeine for cough is relevant to the assessment of benefit/risk profile of these products. This is an incorrect assumption. The prevention of cough is not a TGA approved indication for codeine containing cold and flu products and any decision that is made upon the basis that codeine's role in cold and flu products is for anti-tussive purposes raises questions as to the merits of the decision.

[2] Macquarie University. The value of OTC medicines in Australia. March 2014.
[3] Figures calculated using Macquarie University Consumer Fact Book data (March 2015) and publicly available data on unit costs.

Timing

ASMI calls on the Delegate to defer any final decision until there has been a proper examination of the full impact of the decision (see above).

ASMI calls on the delegate to allow the current review of the Scheduling Policy Framework to conclude before making any final decision affecting codeine.

ASMI calls on the Delegate to allow sufficient time for the prototype real-time monitoring system to be implemented which will provide current, objective, data on which to base a final scheduling decision. ASMI, and other stakeholders who have worked on the development of the monitoring prototype, suggest that a 12 month period of operation would be an appropriate period in which to collect sufficient data.

If, following a proper examination of the impacts, aided by data from the real-time monitoring system, there is a decision to up-schedule codeine containing analgesics, then a 24 to 36 month transition period should be considered (the precise timings to be finalised as part of the RIS process). In relation to *existing* products, sufficient time needs to be allowed for sponsors to revise labelling, update the ARTG entries, exhaust products already in the supply chain and ensure a smooth transition for retailers and consumers. Where sponsors need to develop, register and source *replacement* products, further time will be required together with expedited regulatory pathways.

In addition, it is important to highlight that codeine containing cold and flu preparations are seasonal, with the height of sales in the winter months. To implement an effective date at the height of the cold and flu season after commitments are already locked in, is impractical and will result in millions of dollars' worth of unnecessary write-offs.

ASMI notes that products containing codeine or pseudoephedrine have permits associated with them, which further adds to the transition complexities. On this point, one ASMI member has advised that they typically order codeine products 12-18 months in advance.

Patient risk will also be increased unless sufficient time is allowed for suitable education processes around alternatives to be developed.

An implementation date of 1 June 2016 is therefore not realistic.

Specific concerns with the reasoning of the interim decision

In addition to the above matters, ASMI provides the following comments in relation to specific elements of the interim decision:

<u>Benefit-Risk Assessment</u>

"Purpose is questioned since benefit is low" [pages 11, 12]
"…the addition of codeine adds only a minor additional analgesic effect over and above that of the ibuprofen or paracetamol in the combination product." [page 13]
"There is no evidence that low dose codeine combination analgesics provide any additional analgesia over optimal dosing of paracetamol, aspirin or ibuprofen." [page 14]

"Codeine in the unit doses present in OTC products provides very little additional analgesic effect over and above that provided by the accompanying drug in the combination." [page 15]
"Compound analgesics containing codeine plus paracetamol or codeine plus ibuprofen, show minimal analgesic benefit compared to the simple analgesics (paracetamol or ibuprofen) alone." [page 16]

As these quotes show, the interim decision effectively dismisses the benefits of codeine containing analgesics in terms of their efficacy. It is unclear what level of assessment of the benefit/risk balance was presented in the Evaluator's report to the ACMS, however, Cochrane reviews of paracetamol plus codeine[4] and ibuprofen plus codeine[5] have established that these combinations are effective. Also, clinical studies demonstrate that codeine-containing combination analgesics at OTC doses are more efficacious than placebo[6,7] or single ingredient analgesics.[8,9,10]

The interim decision also effectively dismisses the benefits that consumers obtain by way of timely access to these effective medicines.

The dismissal of the efficacy and access benefits of these products, has led to an incomplete assessment of their benefit/risk profile.

Polymorphic Metabolism

"Risks of medication misadventure through polymorphic metabolism…" [page 11]
"The major impact on public health of the proposed amendment would be a reduction in the risk to those individuals who, unbeknownst to themselves, have a rapid metaboliser phenotype of CYP4502D6 and are therefore at significant risk of excessive morphine concentrations following ingestion of usually recommended doses of codeine for any indication. … Individuals rarely know their metaboliser status, and testing is not readily available." [pages 13 – 14]

The interim decision, assumes that these "ultra-rapid metabolisers" will be identified during the course of the doctor's visit prior to a prescription being issued. There has been no evidence put forward to show that this currently occurs in relation to the codeine products already included in Schedule 4 and there has been no assessment of what impact the increased genetic testing will have on the healthcare system.

We would therefore suggest that the risk of misadventure through polymorphic metabolism is not necessarily mitigated by this decision.

[4] Toms L, Derry S, Moore RA, McQuay HJ. Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. *Cochrane Database Syst Rev* 2009;(1):CD001547.
[5] Derry S, Karlin SM, Moore RA. Single dose oral ibuprofen plus codeine for acute postoperative pain in adults. *Cochrane Database Syst Rev* 2013;3:CD010107.
[6] Frame JW, Fisher SE, Pickvance NJ, Skene AM. A double-blind placebo-controlled comparison of three ibuprofen/codeine combinations and aspirin. *Br J Oral Maxillofac Surg* 1986 April;24(2):122-129.
[7] Daniels SE, Goulder MA, Aspley S, Reader S. A randomised, five-parallel-group, placebo-controlled trial comparing the efficacy and tolerability of analgesic combinations including a novel single-tablet combination of ibuprofen/paracetamol for postoperative dental pain. *Pain* 2011 March;152(3):632-642.
[8] Matts SG. A clinical comparison of Panadeine Co., soluble codeine co., soluble aspirin in the relief of pain. *Br J Clin Pract* 1966 October;20(10):515-517.
[9] Comfort MB, Tse AS, Tsang AC, McGrath C. A study of the comparative efficacy of three common analgesics in the control of pain after third molar surgery under local anaesthesia. *Aust Dent J* 2002 December;47(4):327-330.
[10] Macleod AG, Ashford B, Voltz M, Williams B, Cramond T, Gorta L, Simpson JM. Paracetamol versus paracetamol-codeine in the treatment of post-operative dental pain: a randomized, double-blind, prospective trial. *Aust Dent J 2002* June;47(2):147-151.

Harm

"Increasing amount of evidence for harm from abuse." [pages 11 and 13]
"Anecdotally some abusers of OTC codeine products are consuming 30 to 70 tablets/capsules per day of the CCAs." [page 14]
"The potential for severe adverse effects at "usual" doses in ultra-rapid metabolisers is such that codeine appears to be an unsuitable candidate for OTC availability, with either S2 or S3 scheduling." [page 12]
"Current labelling and packaging include insufficient warnings, and that there should be clear warning labels stating the risks of addiction and dependence, the risks of harm from the paracetamol or ibuprofen, and the risk of death." [page 13]
"Codeine is emerging as an increasingly commonly used drug of abuse internationally and in Australia." [page 13]
"Misuse of OTC codeine products including deaths resulting from hepatic injury, gastrointestinal perforations, hypokalaemia and respiratory depression." [page 13]
"Rescheduling to Schedule 3 has not achieved the required reduction in harm to affected individuals. Since the rescheduling of codeine from 2010 there hasn't been the reduction in risk that might have occurred." [page 15]

The language used in the interim decision creates a clear picture that the harms associated with OTC products containing codeine are likely, serious and widespread. Unfortunately, the interim decision contains no objective evidence that this is the case. Of note, the interim decision does not distinguish between evidence from before and after the re-scheduling of 2010 (from S2 to S3) and does not distinguish OTC codeine products from other prescription products. Without a distinction between the pre- and post-2010 re-scheduling decision there can be no proper analysis of the impact of that re-scheduling.

On the basis of the materials cited in the interim decision (and materials published subsequently), it is not clear whether misuse of codeine containing analgesics has actually increased since the re-scheduling decision of 2010. This is a critical factor that needs to be addressed before any scheduling decision should be made. Without an analysis pre and post the re-scheduling of codeine containing analgesics in 2010, the success or failure of the up-scheduling cannot be assessed properly.

Although the interim decision claims that "*rescheduling to S3 has not achieved the required reduction in harm*" [page 15] and that "*there hasn't been the reduction in risk that might have occurred*" [page 15] there is no comparison of data pre- and post the 2010 re-scheduling and there is no description of the criteria on which these statements are based. ASMI questions how these statements can be made without such a comparison and without such criteria.

Importantly, the interim decision does not describe or explain how changing from S3 to S4 will actually reduce harm. There is no monitoring of prescription medicines and misuse and abuse of prescription medicines already occurs. It is simplistic to assume that placing an obstacle in the way of access overall will solve the problem of misuse in a small proportion of users.

Ibuprofen Plus Paracetamol Combination

"A recently released combination of two non-opioid analgesics (ibuprofen plus paracetamol) appears to be more effective than the CCAs, with a number needed to treat (NNT) of 1.5. This combination would fill any gap left by the unavailability of CCAs over the counter…" [page 13]
"However, pharmacists can recommend alternate pain relief products, such as a paracetamol-ibuprofen combination, or consumers could obtain a prescription (to have on hand when needed for acute pain) if they visit a general practitioner for any reason." [page 17]
"There are alternative OTC analgesic products for short-term pain relief." [page 17]

The interim decision relies heavily on the role of the ibuprofen plus paracetamol combination in satisfying consumer's OTC pain needs. This combination has been on the Australian market since March 2014 and there has still been a demand for S3 codeine containing analgesics. There are a number of patients for whom either ibuprofen or paracetamol is not suitable. For these patients the combination product would not be appropriate, and would mean that the single active analgesic would be their only OTC option.

The assumption that the ibuprofen plus paracetamol combination would address the unmet medical need resulting from a narrowing of the choice of available medication is not supported by evidence. We note that this combination has only been on the market a short time and is currently scheduled as S3. The combination cannot be advertised to consumers. Consumers are unaware of this product as an alternative for moderate pain relief. Pharmacists are very familiar with codeine combinations, they have been on the market for many years. With the current scheduling and awareness of the ibuprofen plus paracetamol combinations, they are not the immediate alternative option that the paper suggests.

These combination products should be seen as an addition to the range of options and not as a replacement for products which are safely and effectively helping people every day.

It is in consumer's best interest to have a range of effective OTC medicines available to them so that they have timely access to pain relief that suits their needs.

The Role of Industry and Pharmacy Organisations

"Rescheduling to Schedule 3 has not achieved the required reduction in harm to affected individuals. Since the rescheduling of codeine from 2010 there hasn't been the reduction in risk that might have occurred." [page 15]
"Since OTC CCAs were rescheduled to Schedule 3 in 2010, industry and pharmacy organisations have not been able to fully address concerns regarding codeine dependence." [page 15]
"Despite the risks of abuse identified when CCAs were up-scheduled in 2010 there has been no initiative to include CCAs into Project Stop prior to the application to up-schedule codeine to S4." [page 17]

As mentioned above, the interim decision contains no examination of the data pre- and post the 2010 re-scheduling. It is therefore hard to understand how the delegate can conclude that there has not been "the required reduction in harm", or there hasn't been the "reduction in risk that might have occurred", or that concerns have not been able to be "fully address[ed]".

This further demonstrates the challenges of the current scheduling framework being fit for purpose and the importance of taking a broader set of factors into consideration in assessing benefit-risk profile.

Labelling

"Changing the labelling and decreasing the pack size will not adequately address the problem of misuse and dependence." [pages 11 and 13]
"*Current labelling and packaging include insufficient warnings, and that there should be clear warning labels stating the risks of addiction and dependence, the risks of harm from the paracetamol or ibuprofen, and the risk of death*." [page 13]
"Another option considered was decreasing the pack size of CCAs from the current limit of five days with a recommended daily dose not exceeding 100 mg of codeine to a pack size limit of three days' supply as has occurred in the United Kingdom. However decreasing the available pack sizes of OTC codeine products might help reduce the incidence of new users becoming dependent on codeine, but is unlikely to be effective for those who are already dependent." [page 17]

In ASMI's view, OTC labelling is the single most important piece of information for consumers as it provides the necessary information to help consumers understand if the medicine is right for them, how to use the medicine safely, and when to seek advice from a pharmacist or doctor.

The TGA's previous labelling consultations have stressed the importance of labelling in terms of Quality Use of Medicines and significant resources are employed to create and test labelling and pack designs that enable consumers to understand how to appropriately use their medicines.

It is therefore surprising that the Delegate has expressed such a lack of confidence in the utility of labelling and label warnings.

As outlined in our initial submission, it is ASMI's view that mandatory label statements on the risk of dependence together with a real-time monitoring system and information resources for pharmacists and consumers represents the optimum way to mitigate the risks of misuse and abuse of codeine containing analgesics.

ASMI notes that in the two most relevant markets (New Zealand and the United Kingdom) regulators have chosen to allow access to codeine containing analgesics without a prescription and have chosen to address the issue of dependence by way of label warnings.

Scheduling Factors

"Codeine does not meet the SPF scheduling factors for inclusion in Schedule 3." [page 16]

ASMI objects strongly to this statement by the Delegate, firstly because it is not correct and secondly because it mistakenly conflates codeine containing analgesics with codeine containing cold and flu products.

In ASMI's view, codeine containing analgesics meet the scheduling factors for Schedule 3 and codeine containing cold and flu products meet the scheduling factors for Schedule 2.

Scheduling Factors – S2

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.*

   The medicine is for minor ailments or symptoms that can easily be recognised and are unlikely to be confused by the consumer with other more serious diseases or conditions. Treatment can be managed by the consumer without the need for medical intervention. However, the availability of a pharmacist at the point of sale supports the consumer in selecting and using the appropriate medicine.

   Consumers are able to recognise the symptoms of cold and flu and manage their treatment.

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.

   The safety of these combinations products is well established and there is no evidence of actual or potential misuse.

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.

   There is no evidence of actual or potential misuse or dependency.

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.

   The safety of these combination products is well established and adequate warnings appear on the labelling.

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.

   These combination products are for short-term, symptomatic relief of self-limiting conditions.

Scheduling Factors – S3

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.

   Consumers are able to recognise the pain and manage short-term treatment.

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.*

   At established therapeutic doses, and for short-term use, dependency is not expected.

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.*

   The risks are known and can be managed 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.

   The products are intended for short-term pain relief.

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.

   The products are intended for short-term pain relief.

Monitoring

"Project Stop relates to the monitoring of sales of pseudoephedrine and is a police related activity to prevent diversion of pseudoephedrine as a precursor for illegal methamphetamine manufacture." [page 17]
"Real-time monitoring of medicines is not currently in place in any jurisdiction other than Tasmania where it is restricted to S8 medicines. There is no formal implementation of real-time monitoring across Australia and whether its implementation would it is unsure whether it would ever come down to S3 medicines." [page 17]
"In both Project Stop and real-time monitoring the onus on prevention of supplying CCAs would fall on pharmacists when dealing directly with consumers." [page 17]

The Delegate appears to be concerned that the onus of prevention of supply should fall on pharmacists, however there is no explanation as to the basis for such a concern. Pharmacists currently have this onus under Project STOP and there has been no suggestion that there are problems with their oversight.

These comments from the Delegate also appear to misunderstand the real-time monitoring system that is being proposed. ASMI, Pain Australia, The Pharmacy Guild of Australia and Pharmaceutical Society of Australia have collectively developed a prototype national real-time-monitoring system for S3 codeine containing analgesics.

This monitoring system would be separate to Project STOP, but would provide a similar function in standardising the pharmacist's interaction with patients and in recording the patient's recent purchase history. It would also provide a simple means for referral of patients to pain specialists if chronic use is identified

Although initially confined to S3 codeine containing analgesics, the system could be expanded to cover other pharmacy services and could also permit access by other healthcare professionals in the future.

As the Delegate notes, there is no corresponding system in place for prescription analgesics.

ASMI, wishes to advise the Delegate that if the S3 codeine containing analgesics are up-scheduled then work on the prototype system will likely cease.

Up-scheduling will therefore remove the impetus for developing a national monitoring system for codeine containing analgesics which are at risk of misuse and abuse. Given the lack of a system for prescription medicines this will not address the risk of patients "doctor shopping" for access to medication.

Scheduling Factors in summary

Section 52E(1)(a) - Risks and benefits

- Benefits:
    - OTC Codeine containing analgesics offer an option for consumers to treat short term moderate pain particularly when single ingredient analgesics do not provide adequate relief. Clinical studies have shown that OTC codeine containing combination analgesics are more efficacious than placebo and single ingredient analgesics.[11,12]
    - 5 day pack does not on its own cause dependence or abuse. When used as directed for a short duration, these products have a good safety profile.
    - Availability from pharmacists ensures advice and availability when needed, without the need for an appointment and associated Medicare costs. Pharmacists have a Protocol for supply as well as consumer educational material and front of pack labels to allow them to more easily raise the subject of inappropriate use with consumers. Pharmacists can refer when needed.
- Risks:
    - The reported risks of dependence and abuse particularly with excessive use over a prolonged period of time. Prolonged use at supra-therapeutic doses can lead to harm.
    - For some people, differences in drug metabolism mean that there can be variability in response, which alters efficacy and tolerability.

Section 52E(1)(b) – Purposes for use and extent of use

- Indicated for short term use for moderate to severe pain associated with headache, dental pain and other types of pain.
- Front of pack labelling provides instructions that the products are for three days use only and that codeine can be addictive.

Section 52E(1)(c) – Toxicity

- Toxicity typically occurs with longer term use at higher than recommended doses, following dependence or misuse.
- The type of harm seen is usually dependent on the non-opiate analgesic that forms part of the combination (ibuprofen, paracetamol)

Section 52E(1)(d) - Dosage, formulation, labelling, packaging and presentation

- Supply is limited to 5 days use. The products are intended for short term use.
- Labelling of many branded products will include warning statements consistent with those used in the UK, such as “Can cause addiction. Do not use for more than 3 days” following

[11] Toms L, Derry S, Moore RA, McQuay HJ. Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. Cochrane Database Syst Rev 2009; (1):CD001547
[12] Derry S, Karlin SM, Moore RA. Single dose oral ibuprofen plus codeine for acute postoperative pain in adults. Cochrane Database Syst Rev 2013;(3):CD010107

voluntary implementation by some ASMI member companies. This is already being phased in and should be mandated.

- Pharmacists have updated their supply protocol, undertaken educational activities and now are required to use a Cautionary and Advisory Label following the inclusion of OTC codeine containing analgesic warning statements in the APF 23. Consumer education leaflets are also provided as part of these measures.

Section 52E(1)(e) - Potential for abuse

- A five day pack on its own is not an instigator of addiction.
- The risk of dependence and abuse increases if the products are taken for prolonged periods at higher doses than recommended.
- A real-time reporting system such as that used for pseudoephedrine is likely to be a very effective way to mitigate risk, by identifying pharmacy shoppers and targeting those who require referral for specialised care.

Section 52E(1)(f) - Other matters

- The newly implemented PSA initiatives will all serve to enable more effective interaction with customers, provide an avenue to educate and counsel them and thereby mitigate risks. The need to educate consumers will be the same regardless of the scheduling.
- These measures, coupled with universal adoption of label warnings and a real time reporting system will be the most effective way of targeting the individuals most at risk while not inconveniencing or increasing costs for people who use the products appropriately.

Overseas Regulatory Status

- Concerns about harms associated with dependence, abuse and misuse are not limited to Australia.
- Other comparable regulatory authorities have assessed these matters in reviews of safety and classification
- Low dose codeine containing analgesics are classified as Pharmacy Medicines in some key markets:
    - UK: Pharmacy Medicines with the mandatory labelling warning statements described above. Pack size limited to three days.
    - New Zealand
    - Canada
    - Denmark
    - France
    - Ireland
    - South Africa, which also has a real time monitoring system

The Delegate's interim decision refers to the prescription status of codeine in the USA, but does not provide the context that no equivalent of a 'pharmacist only category' exists in that territory, thus non-prescription products are generally freely available. Furthermore, prescription medicines in the USA can be advertised direct to consumers. Thus any comparisons to the USA are not relevant to considerations of benefit/risk in the Australian environment.

As an unintended consequence of a change in scheduling in Australia, it should be recognised that based on the common use of harmonised packs with New Zealand patients in New Zealand may experience difficulty obtaining products leaving an unmet medical need due to the narrowing of product options available.

Conclusions

OTC codeine containing analgesics

ASMI believes that the current scheduling of OTC codeine containing analgesics is appropriate. The majority of consumers use the product responsibly for the short term treatment of moderate to severe pain for self-limiting conditions. In relation to the sales of the products, the number of cases of harm from addiction is low in comparison – indicating that while the harms are significant for those affected and those who treat them, the problem is not widespread so more specific and targeted interventions are needed to address those at most risk.

ASMI does not believe that a move to Schedule 4 provides a simple solution which will solve the problems that can arise as a result of misuse or addiction. ASMI takes the issue of harm very seriously and supports the new education and counselling initiatives undertaken by pharmacists, the new Cautionary & Advisory labelling of the APF 23 as well as more effective monitoring which could be achieved by a real time monitoring system such as a modified Project STOP system. This would enable better detection and referral of vulnerable people while not inconveniencing those who use the products correctly. Many ASMI members have voluntarily implemented prominent front of pack warning statements on the risk of addiction and a treatment duration of 3 days use.

As part of Schedule 3 supply requirements, pharmacists must provide consumers with counselling and advice on use of these products and ensure that supply is in accordance with the protocol for supply. Should these products be up-scheduled, then the legitimate users of these products will require a prescription – which will be costly, inconvenient and most likely result in purchase of a larger quantity on prescription (e.g. 30 or 50 tablets), and this in itself may predispose to use for longer than needed.

OTC Cold and Flu products containing codeine

ASMI believes that the current scheduling of cold and flu products is appropriate. These products are not labelled or marketed as analgesics. No evidence has been provided that these products are being misused and no information has been made available on the basis of the scheduling proposal.

ASMI assumes that the proposal is based on a hypothetical risk that misuse may occur by those who are misusing codeine. There is no evidence to support this position and sales data indicates that the product usage is predominantly seasonal and there has been no indication of a growth in demand since the codeine containing analgesics were rescheduled to Schedule 3 in 2010.

Recommendations

Considering the magnitude of the impact of the decision a deferral in making a final decision is urgently required to ensure a full and transparent process is implemented.

ASMI calls on the Delegate to re-examine the decision to apply the same scheduling changes to codeine containing cold and flu products as to codeine containing analgesics. The current scheduling of codeine containing cold and flu products remains appropriate and there should be no change to the scheduling of these products.

ASMI calls on the Delegate to defer making a final decision in relation to codeine containing analgesics until:

1. A real-time monitoring system has been put in place and sufficient data collected,
2. A comprehensive examination of the impacts of the decision in the form of a Regulation Impact Statement (RIS) has been conducted, and,
3. The acknowledged shortcomings of the current Scheduling Policy Framework have been addressed.

As an industry representative, ASMI is a key stakeholder in scheduling matters and we are keen to provide further input as required. We look forward to a final decision which appropriately reflects the risks and benefits of codeine containing products.

Please contact me should you require any further clarification relating to this response.

Yours sincerely,

[redacted]

From: TGA Info
To: Medicines Scheduling
Subject: FW: Contacting the TGA [SEC=UNCLASSIFIED]
Date: Friday, 16 October 2015 11:58:32 AM

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]
Regulatory Services and Improvement Branch

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

Therapeutic Goods Administration
Department of Health
PO Box 100
Woden ACT 2606 Australia
www.tga.gov.au
-----Original Message-----
From: [redacted]
To: TGA Info
Subject: Contacting the TGA

I would just like to be added to the petition to stop the pain killers and cold and flu tablets from only being able to be bought via a prescription. Besides from the fact that it will clog up the medical system and cost more valuable tax payer money, it will mean that people who do have full time jobs will need to take time off work to go to a doctor to get a perscription for something so simple that could be fixed by a simple trip to the chemist. People don't have time to waste doing this...the other issue is with the risk of catching other virus' from the doctors waiting room therefore needing more time off work. It's absolutely ridiculous that Australian citizens need to be 'babysat' and can't make decisions for themselves and their own well being. I don't need a call back unless necessary to put me onto the register. Thank you

Kind Regards
[redacted]

The Pharmacy Guild of Australia

Interim decision & reasons for decisions by delegates of the secretary to the Department of Health

Comments by the Pharmacy Guild of Australia to the proposed amendments referred by the delegate for scheduling advice

Codeine

October 2015

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CONTENTS

INTERIM DECISION 1.1 – CODEINE – AMENDMENTS TO SCHEDULE 2 AND 3 ENTRIES

Interim Decision: The delegate's Interim Decision is to delete the current Schedule 2 and 3 entries for codeine and amend the current Schedule 4 and 8 entries to reflect this change.

Overview

The Pharmacy Guild of Australia (the Guild) is opposed to the Interim Decision. As stated in our pre-ACMS meeting submission, it is the view of the Guild that the proposed rescheduling changes are a blunt instrument to address misuse and abuse of these medicines. The Guild believes that the proposal would not only be ineffective at addressing concerns of abuse, but could also have unintended consequences such as:

- For the large majority of people who use these products safely and effectively, rescheduling will make pain relief medicines more expensive and more difficult to obtain;

- Rescheduling codeine will result in substantial costs to the Medicare Benefits Schedule (MBS) through an increase in medical practitioner visits. There will be an increase in the workload of medical practitioners and increased waiting times for patients, especially as many medical practices have limited capacity to accept new patients. Patients who reside in regional, rural and remote areas would be most impacted, given the time and cost to visit a medical practitioner is substantially greater compared to metropolitan areas.[1]

- The decision is likely to have cost implications for the Pharmaceutical Benefits Scheme (PBS), particularly if medical practitioners elect to prescribe consumers higher strength codeine products or other opioids listed on the PBS;

- For patients who do not have ready or affordable access to a medical practitioner, their pain management may go untreated and/or lead to an increase of presentations at hospitals.

The Guild acknowledges the concerns relating to patient safety due to misuse of combination codeine analgesics (CCA) and agrees some action needs to be taken. However, the Guild contends the implementation of a mandatory real-time monitoring system in community pharmacy would be more effective and economical to assist in identifying at-risk consumers, facilitate access to education materials and support appropriate referral when required.

Since the August ACMS meeting, the Guild, in partnership with the Australian Self Medication Industry (ASMI), has developed a prototype real-time monitoring system specifically designed to record and track pharmacy provision of over-the-counter (OTC) products containing codeine. Unlike the current Project STOP system, which is primarily a law enforcement tool to prevent diversion of pseudoephedrine, the prototype system will also be a clinical decision support system, assisting pharmacists in identifying patients who are risk of codeine dependence. The system will also have the capacity for pharmacists to record clinical notes and provide guidance regarding suitable referral pathways to help patients better manage their pain and enhance health outcomes.

The prototype real-time monitoring system is explained further in the next section. The Guild and ASMI are confident that the full system can be developed and operating in community pharmacies by June

[1] National Health Performance Authority Media Release 01 October 2015 – People 2 to 3 times more likely to avoid seeing a GP die to cost in some areas

2016, which is the current implementation date for Interim Decision to take effect. The introduction of this system should be complemented by a series of additional measures such as:

- Mandatory warning labels advising consumers of the potential for dependence from prolonged use of these products (greater than 3 days);
- Reduction of pack sizes for these products to a maximum of 3 days' supply;
- Ongoing education for pharmacists, and
- A consumer awareness campaign.
-

In order to allow time for new real-time monitoring system to be developed and deployed as well as its impact on detecting abuse/misuse analysed and evaluated, **the Guild requests the delegate defers the final decision on changes to the Schedule 2 and Schedule 3 entries for codeine for at least 12 months.**

Key points responding to the Interim Decision are as follows:

1. **The risks and benefits of the use of a substance**

    i. There is evidence that indicates that codeine in OTC doses can offer superior analgesic effects compared to other available OTC analgesics.

    ii. Therapeutic guidelines and product information for OTC codeine products usually require patients to take at least two tablets every 4-6 hours. Therefore a patient who is taking a product containing 12-15mg of codeine for mild to moderate pain receives a dose of codeine that is roughly equivalent to the amount they would receive taking a prescription codeine product for the same indication.

    iii. There is no evidence to suggest cough and flu preparations are subject to abuse/misuse and the Interim Decision to reschedule these products appears to be based primarily on the purported risk and benefits (efficacy). If the evidence indicates that the risk/benefit profile is not favourable, then the matter should be referred to the relevant section of the Therapeutic Goods Administration (TGA) who can assess whether these products should remain on the Register of Therapeutic Goods. The Guild believes the TGA conducting a comprehensive assessment regarding the risk/benefit profile of codeine is more appropriate than rescheduling in this context as the overall risk/benefit profile of cough and cold products containing codeine will not change based purely on rescheduling.

    iv. If codeine is completely removed from Schedule 3, a significant proportion of patients who are currently taking paracetamol/codeine combination products would not be able to effectively and safely treat their condition as other OTC products such as a combination product containing a non-steroidal anti-inflammatory drug (NSAID) are unsuitable. Hence they will have little choice but to obtain a prescription medicine analgesic.

2. **The toxicity of a substance**

    i. Given the statement made in the Interim Decision that it is not practical to ascertain a patient's metaboliser status, the Guild queries why this argument is emphasised as a justification for rescheduling. Rescheduling will restrict access to the majority of patients who are not poor/ultra-metabolisers while offering no additional safeguards for patients who are. In this context, the Guild believes that the risks of harm to a very small number of individuals needs to be balanced against of the vast majority of patients who use these products safely and effectively, particularly given the risk of harm cannot be mitigated purely through rescheduling.

ii. A new pharmacy initiative would enable pharmacists and medical practitioners to work together so that a patient's CYP2D6 status can readily be obtained. Further information can be found in **Attachment 2**.

3. The potential for abuse of a substance

i. Codeine in Schedule 3 products are only indicated for the treatment of acute pain and are sold in small packs (maximum 5 days' supply). The evidence suggests taking Schedule 3 codeine medicines when used as directed to treat episodic or acute pain at the maximum daily dose and maximum treatment period has a little risk of producing dependency.

ii. Rescheduling will not address issues of misuse and abuse.

4. Any other matters that the Secretary considers necessary to protect public health

i. The Guild does not believe the full consequences and disadvantages of this scheduling decision have been properly considered.

ii. Given the sheer magnitude and extent of the impact the proposed scheduling amendment will cause to a wide range of stakeholders, the Guild believes it is imperative that a formal Regulatory Impact Statement (RIS) be conducted prior to any final decision on rescheduling.

Guild recommendations

1. The final decision on codeine be deferred for at least 12 months so that a real-time monitoring system can be implemented and deployed and its impact on detecting abuse/misuse analysed and evaluated.

2. State and Territory Governments as a matter of urgency amend their medicines and poisons regulations where applicable to mandate the online real-time recording of codeine in their respective jurisdictions.

3. The introduction of a real-time monitoring system should be complemented with additional measures such as:

   I. Mandatory warning labels advising consumers of the potential for dependence from prolonged use of these products (greater than 3 days);
   II. Consideration to reduce pack sizes for these products to a maximum of 3 days' supply;
   III. Ongoing education for pharmacists, and
   IV. A consumer awareness campaign.

4. If the evidence indicates that the risk/benefit profile of a product is not favourable, then the matter should be referred to the relevant section of the TGA who can assess whether these products should remain on the Register of Therapeutic Goods. The Guild does not believe this is a relevant factor in determining scheduling (re)classifications.

5. Given the widespread implications and cost of the rescheduling proposal, it is imperative that a formal Regulatory Impact Statement (RIS) must be conducted prior to any final decision on rescheduling. This RIS should also examine the comparative risk/benefits of implementing a national real-time monitoring system as an alternative strategy.

Real-time Monitoring System for codeine

The Guild, in partnership with ASMI, have been working with the Guild's IT subsidiary (GuildLink) regarding the development of prototype real-time monitoring system suitable for recording products containing codeine. GuildLink have extensive experience in this area, having operational oversight for Project STOP, a real-time monitoring system currently used in pharmacies to record and track sales of products containing pseudoephedrine. Project STOP has been an effective tool in reducing the diversion of locally sourced pseudoephedrine while maintaining OTC access for patients using the product appropriately for legitimate use. In the absence of such a system, it is highly likely pseudoephedrine would have become a prescription medicine, as is the case in New Zealand where real-time recording of such products does not exist.

The system has the full support of law enforcement agencies in each State/Territory as it provides valuable information that assists in their investigations to identify:

- recidivist purchasers' of products – leading to the commencement of investigations;
- criminal syndicates/networks; and
- Identify 'runner' or 'pseudo runners' who will lead investigations to the drug manufacturers.

State/Territory Health departments have also utilised Project STOP to monitor the compliance of requirements for supplying pseudoephedrine.

Current real-time monitoring system – Project STOP

The Project STOP system was mentioned as part of the Interim Decision which specifically stated:

> *Despite the risks of abuse identified when CCAs were up-scheduled in 2010 there has been no initiative to include CCAs into Project Stop prior to the application to up-schedule codeine to S4.*[2]
>
> *Since OTC CCAs were rescheduled to Schedule 3 in 2010, industry and pharmacy organisations have not been able to fully address concerns regarding codeine dependence.*[3]

The Guild makes the following comments in relation to these points:

- **Technical Constraints** - The Project STOP system was designed solely to record pseudoephedrine sales, in order to prevent these types of products being diverted to the manufacturing of methamphetamines. Project STOP was primarily developed in 2005 and 2006 with moderate changes in 2008 and 2009 hence the technologies, techniques and frameworks utilised in Project STOP are now significantly old in technology terms. Incorporating other products into the Project STOP would pose a significant risk of breaking existing functionality and thus jeopardising the system's existing role of tracking pseudoephedrine.

- **Legal Constraints** – As mentioned, the primary purpose of the Project STOP system is to assist in law enforcement (preventing diversion of pseudoephedrine) and information recorded in this system is accessed by law enforcement agencies and health regulators. In contrast, the abuse/misuse of codeine products is a clinical issue rather than a law enforcement issue. Pharmacists would be in breach of the Project STOP User Agreement and privacy laws if they record requests and purchases of non-pseudoephedrine Schedule 3 medicines without explicitly detailing all relevant information to patients. This is not practical for pharmacists to convey this lengthy and complex information to every individual patient.

[2] Interim decisions & reasons for decisions by delegates of the Secretary to the Department of Health – October 2015, 17
[3] IBID, 15

- **Government inaction** – The Guild has for many years advocated for the implementation of a real-time system to address issues of abuse/misuse. In our submissions in 2009 and 2010 to the then National Drugs and Poisons Scheduling Committee (NDPSC) considering the re-scheduling of OTC CCAs from Schedule 2 to Schedule 3, the Guild advocated for a real-time monitoring system to provide pharmacists with a clinical decision support tool, noting that re-scheduling alone was a blunt instrument.

  The Guild disseminates information to Guild members regarding appropriate supply of these products and reminding pharmacists of their obligations under the relevant Pharmacy Board Guidelines. However, Governments must play a role in determining and implementing effective changes/initiatives to address matters relevant to public health (such as codeine abuse/misuse) in consultation with stakeholders.

  While the Guild stands ready to assist Governments on such matters, it is ultimately Governments that have to make the necessary legislative changes and create the regulatory environment in order for real-time monitoring system to operate at optimal effectiveness. To date, no Government at any level has initiated discussions with the Guild to discuss concerns regarding codeine dependence and the implementation of a real-time monitoring system. This is in spite of all Governments being aware about this problem.

  The National Pharmaceutical Drug Misuse Action Framework (The Framework), endorsed in 2012 by Commonwealth, State and Territory Health Ministers, stated that painkillers and tranquillisers were causing increasing addiction, overdoses, trafficking and crime. The Framework recommended smaller pack sizes, more support for pharmacists, and the overdue launch of a national electronic recording and reporting of controlled drugs (ERRCD) system, providing real-time alerts about products such as codeine and higher risk script items.

  Despite this Framework, very little has actually been implemented. Even straight forward measures such as State/Territory Governments making legislative amendments to mandate the recording of codeine has not taken place.

  The Guild notes that despite Project STOP's success in preventing diversion of locally sourced pseudoephedrine, no Government currently provides any funding towards the maintenance of this vital system, despite the Guild's repeated requests.[4] Furthermore, there are a number of jurisdictions where the recording of pseudoephedrine in an online real-time system is not mandatory, again in spite of the Guild's repeated advocacy in having national consistency on this matter.

  The Guild is ultimately restricted in its ability to assist in addressing concerns relevant to pharmacy and public health if Governments are unwilling to offer support. The Guild therefore rejects the inference suggested in the Interim Decision that addressing codeine dependence is purely the responsibility of pharmacy and industry organisations with Governments having no role.

Proposed new real-time monitoring system for codeine – prototype

In recognition of concerns regarding abuse/misuse and the urgency of the need for such a system, the Guild has elected to develop a prototype of a new real-time monitoring system designed as a clinical decision support tool that when fully operational, will be accessible across pharmacies nationally. The Guild will conduct broader consultation with a range of stakeholders including consumer groups, State/Territory health departments, industry during the development and implementation phase.

[4] The Commonwealth Attorney-General's department provided funding for the initial national roll-out of the system in 2007.

As mentioned in our pre-meeting submission a consumer survey conducted by the Guild in April 2015 found the majority of respondents (95 per cent) indicated they were prepared to have their details recorded when purchasing codeine combination products if this meant these products would remain available over-the-counter.

System Overview

Attachment 1 details the high level system workflow. Prior to recording a product in this system, a pharmacist will have first determined through an initial discussion with the patient, that a codeine appropriate is suitable. The pharmacist will then enter the patient's identification details into the system to view records of previous use and any clinical notes recorded by other pharmacists. These records will provide the pharmacist with additional information to determine whether a codeine product is therapeutically appropriate. The pharmacist will then record the details of the current transaction (allowed, denied or safety sale) including clinical information in relation to reason(s) for use, recommended duration of use and any follow up referral actions. Detailed screen shots of each individual step in the workflow is also included in the attachment.

Privacy considerations

Recording of patient details is based on patient consent and reflect the Australian Privacy Principles Guidelines.[5]

If a patient does not grant their consent, their details will not be recorded on the system. Equally, a pharmacist can elect not to supply codeine products to these patients and instead recommend an alternative non-codeine product or treatment option (e.g. referral option).

Storage of information

The new system will record similar information that is recorded under the existing Project STOP system. Specifically the system will record:

- The name of the product (including specific pack size);
- Where a product was purchased previously (pharmacy postcode);
- The patient's unique identification number (e.g. driver's licence number); and
- Whether previous purchase requests were allowed, denied or processed as a safety sale.

In addition, the new system will also record clinical information such as:

- The reason for use (e.g. neck pain, back pain, post-surgical);
- Recommendations regarding length of use; and
- Whether any follow up actions have been provided to the patient (e.g. referral to medical practitioner, pain management plan).

Pharmacists will be able to view all records associated with the patient's identification number to confirm the therapeutic need for the medicine and that the treatment is or remains appropriate for the specific pain condition and that the patient continues to use the medicine safely and appropriately. If a problem or risk is identified, the pharmacist can record any interventions provided within their scope of practice as well as any referrals to other health care professionals.

[5] Privacy Fact sheet 20: Consent and the handling information in your eHealth record

Pharmacy uptake of system

Currently, over 80 per cent of pharmacies across Australia are registered to use Project STOP to record pseudoephedrine supply. Even in states where the recording of pseudoephedrine is not mandatory (such as Victoria and Tasmania), take up of the system in those jurisdictions is still high with 79 per cent and 90 per cent registration rates respectively. Pharmacists are already familiar with the real-time recording of medicines containing pseudoephedrine through Project STOP, hence they will be able to adapt quickly to the new system. Therefore the Guild is confident of the high uptake of the proposed new system as soon as it becomes available.

However, it is still imperative that State/Territory amend their medicines and poisons regulations to mandate the real-time online recording of OTC codeine products. This will ensure universal coverage of the system in pharmacies throughout the country.

Summary

The Guild is confident that the full system can be developed and operating in community pharmacies by June 2016, which is the current implementation date for Interim Decision to take effect. In order to allow time for new real-time monitoring system to be developed and deployed as well as collection and analysis of data from the system, the Guild requests the scheduling delegate defers the final decision on changes to the Schedule 2 and Schedule 3 entries for codeine for at least 12 months.

In order to maximise the effectiveness of a real-time monitoring system, the Guild advocates as a matter of urgency for the States and Territories to amend their medicines and poisons regulations to mandate the real-time online recording of codeine in their respective jurisdictions.

Recommendation

The final decision on codeine be deferred for at least 12 months so that a real-time monitoring system can be implemented and deployed and its impact on detecting abuse/misuse analysed and evaluated.

State and Territory Governments as a matter of priority amend their medicines and poisons regulations where applicable to mandate the electronic recording of codeine in their respective jurisdictions.

Guild responses to specific parts of Interim Decision

Responses are categorised according to the relevant sections under 52E (1) of the Therapeutic Goods Act.

The risks and benefits of the use of a substance[6]

The following statements are made in the Interim Decision:

> *There is no evidence that low dose codeine combination analgesics provide any additional analgesia over optimal dosing of paracetamol, aspirin or ibuprofen*[7]

[6] Section 52E(1a)- *Therapeutic Goods Act 1989*

> *Central consideration in allowing OTC supply of codeine combinations was that the benefits outweighed the risks and therefore asserted that the insufficient data on efficacy may mean that the benefits no longer outweighed the risks. While agreeing that efficacy remains important to any case justifying OTC supply of codeine, the Committee noted the Codeine Working Party advice that there was not sufficient information available to the Members at this time to resolve the question of codeine efficacy at ≤ 30mg.*[8]

The Guild questions the veracity of these statements given there are studies that indicate that while the analgesic effect between paracetamol-codeine combinations and paracetamol alone is small, it has been found to be statistically significant in dosages ranging between 10 to 60mg codeine and 400 to 1000mg paracetamol.[9] [10] Other studies have indicated paracetamol (350mg) in combination codeine (20mg) has a superior analgesic effect to aspirin (500mg).[11]

The vast majority of studies do not examine the efficacy of codeine in doses below 30mg. The Guild believes this is due to the fact that for the treatment of mild to moderate pain, patients will generally be advised by pharmacists to take at least two tablets (in accordance with the therapeutic guidelines and product information) and thus will in fact receive a dose of codeine that is roughly equivalent to the amount they would receive taking a prescription codeine product for the same indication. For example, the product information (PI) for Panadeine Extra ® (Schedule 3) and Panadeine Forte ® (Schedule 4) recommend the same dosage of codeine for mild to moderate pain (two tablets every 4-6 hours for Panedeine Extra ®, 1 tablet over the same period for Panadeine Forte ®, with the Panadeine Forte ® PI only recommending taking 2 tablets for severe pain.[12] [13] Therefore if the guidelines are followed for the treatment of mild to moderate pain, patients will receive the same amount of codeine and double the amount of paracetamol taking Panadeine Extra ® compared to taking Panadeine Forte ®.

Furthermore, the introduction of a real-time monitoring system for OTC CCAs combined with reducing individual Schedule 3 product packs to 3 days' supply, the likelihood of excessive and/or long-term use without intervention and review will be significantly reduced.

Rescheduling of cold/flu preparations (Schedule 2)

As indicated in our pre-meeting submission, the Guild is not aware of any evidence that indicates Schedule 2 phenylephrine products and Schedule 3 pseudoephedrine products containing codeine are subject to abuse/misuse.

As noted in the Interim Decision, the scheduling of codeine for cough and cold preparations was reviewed by the NDPSC in 2009 and the Scheduling delegate in 2011 as part of the cold and cold preparation review. On both occasions the Schedule 2 entry for codeine was deemed as appropriate.[14]
In spite of these previous findings, the decision to delete the Schedule 2 entry for codeine appears to be based primarily on the following statement:

> *The risk/benefit profile for codeine in doses of 8mg – 15mg per dosing unit in combination with other analgesics is unfavourable. There is also a lack of evidence of any benefit of codeine over*

[7] Interim decisions & reasons for decisions by delegates of the Secretary to the Department of Health – October 2015, 14
[8] IBID, 14-15
[9] De Craen, A. J., Di Giulio, G., Lampe-Schoenmaeckers, A. J., Kessels, A. G., & Kleijnen, J. (1996). Analgesic efficacy and safety of paracetamol-codeine combinations versus paracetamol alone: a systematic review. *BMJ*, *313*(7053), 321-325.
[10] Macleod, A. G., Ashford, B., Voltz, M., Williams, B., Cramond, T., Gorta, L., & Simpson, J. M. (2002). Paracetamol Versus Paracetamol-Codeine in the Treatment of Post-Operative Dental Pain: A Randomized, Double-Blind, Prospective Trial. *Australian dental journal*, *47*(2), 147-151.
[11] Sveen, K., & Gilhuus-Moe, O. (1975). Paracetamol/codeine in relieving pain following removal of impacted mandibular third molars. *International journal of oral surgery*, *4*(6), 258-266.
[12] MIMs online – Panadeine Extra
[13] MIMs online – Panedeine Forte
[14] Interim decisions & reasons for decisions by delegates of the Secretary to the Department of Health – October 2015, 10

placebo in the relief of cough, making the risk/benefit profile for this indication unfavourable also. [15]

The Interim Decision to reschedule these products appears to be based primarily on the purported risk and benefits (efficacy). The Guild queries why this is presented as a key justification for changing the Schedule 2 entry of codeine. The risk/benefit profile will not change based on rescheduling to Schedule 4. If the evidence indicates that the risk/benefit profile is not favourable, then the matter should be referred to the relevant section of the TGA who can assess whether these products should remain on the Register of Therapeutic Goods. The Guild notes this occurred previously with dextropropoxyphene in 2011. This eventually led to more stringent oversight regarding the supply of this medicine.[16] The Guild believes this is the appropriate course of action in this context, rather than rescheduling.

In the interim, if there are immediate concerns regarding the abuse/misuse of these particular codeine products, the Guild suggests they are moved to Schedule 3 in order to be encapsulated in the real-time recording system.

Recommendation

If the evidence indicates that the risk/benefit profile of a product is not favourable, then the matter should be referred to the relevant section of the TGA who can assess whether these products should remain on the register of therapeutic goods. The Guild does not believe this is a relevant factor in determining scheduling (re)classifications.

Use of alternative OTC analgesics

The Interim Decision raised several points in relation to alternative options for patients who are currently taking OTC codeine products:

Codeine in the unit doses present in OTC products provides very little additional analgesic effect over and above that provided by the accompanying drug in the combination. It is also noted that there are new combination products with paracetamol and ibuprofen which are more efficacious than low dose CCAs. [17]

A number of the pre-meeting submissions considered it unduly burdensome to require consumers to obtain a prescription for supply of codeine combination analgesics. However, pharmacists can recommend alternate pain relief products, such as a paracetamol-ibuprofen combination, or consumers could obtain a prescription (to have on hand when needed for acute pain) if they visit a general practitioner for any reason.[18]

Of the current products supplied without prescription for the treatment of mild to moderate pain, if CCAs are up-scheduled, the remaining options for use by patients or recommendation by pharmacists are aspirin, ibuprofen or paracetamol as single ingredients (all with unrestricted availability from supermarkets and service stations in small pack sizes), combination ibuprofen/paracetamol or paracetamol/caffeine products, and some other NSAIDs such as diclofenac, naproxen and mefanamic acid.

The NPS MedicineWise[19] indicates aspirin may not be suitable for people who:

- are pregnant;
- have or have a history of stomach ulcers;

[15] IBID, 12
[16] https://www.tga.gov.au/media-release/update-tga-decision-cancel-prescription-pain-killers-19-september-2013
[17] Interim decisions & reasons for decisions by delegates of the Secretary to the Department of Health – October 2015, 15
[18] IBID, 17
[19] http://www.nps.org.au/medicines/pain-relief/simple-pain-reliever-and-fever-medicines/aspirin/for-individuals/who-can-take-aspirin

- have a condition causing them to bleed easily;
- have liver problems;
- have asthma;
- have heart failure; or
- high blood pressure.

Apart from being allergic to paracatamol, the NPS MedicineWise[20] advises people with kidney or liver problems, or those with an alcohol dependency to talk to their medical practitioner or pharmacist before taking paracetamol.

The NPSMedicineWise[21] indicates **ibuprofen and other NSAIDs** may not be suitable for:

- people with stomach problems such as ulcers or bleeding;
- people with heart or kidney problems;
- people with high blood pressure.

Ibuprofen is also not recommended for patients aged over 65 years (unless on the advice of a medical practitioner) and this is a required advisory statement that must appear on all products. [22]

Ibuprofen (and all NSAIDs) can also interact with other classes of medicines including[23]:

- medicines that can increase the risk of bleeding (e.g. warfarin);
- medicines for high blood pressure (anti-hypertensives) and heart failure; ibuprofen and other NSAIDs can cause fluid retention and raise a patient's blood pressure;
- medicines that may affect kidney function (this may increase the chance of kidney problems with ibuprofen);
- medicines that are removed from the body via the kidney; NSAIDs can affect kidney function and so the amount of these other medicines in the body may rise more than it should, increasing a patient's chance of side effects; and
- medicines that can raise potassium levels in the blood (e.g. ACE inhibitors, used to treat high blood pressure); NSAIDs such as ibuprofen can also raise a patient's potassium levels, requiring monitoring by a medical practitioner.

In addition, a TGA safety review of NSAIDs conducted in 2014 found while use of NSAIDs at prescription-only dosages was already known to increase the risk of high blood pressure, heart failure, heart attack and stroke, the TGA NSAIDs review found that these risks also applied to OTC forms of diclofenac, naproxen and ibuprofen. This led to the mandating of additional warning labels on OTC products.[24]

Combination ibuprofen/paracetamol is not suitable for all patients as some patients cannot use either paracetamol or ibuprofen. A study conducted in Australia indicated the proportion of patients who had some form of contraindication, warning or precaution was close to 25 per cent for ibuprofen and 2 per cent for paracetamol.[25] It is interesting to note that this is a higher proportion than those at risk of codeine

[20] http://www.nps.org.au/medicines/pain-relief/simple-pain-reliever-and-fever-medicines/paracetamol/for-individuals/who-can-take-paracetamol
[21] http://www.nps.org.au/medicines/muscles-bones-and-joints/anti-inflammatory-medicines-nsaids/ibuprofen/for-individuals/who-can-take-ibuprofen
[22] Medicines Advisory Statements Specification 2014 – Ibuprofen https://www.comlaw.gov.au/Details/F2014L00693
[23] http://www.nps.org.au/medicines/muscles-bones-and-joints/anti-inflammatory-medicines-nsaids/ibuprofen/for-individuals/interactions-with-ibuprofen
[24] https://www.tga.gov.au/alert/non-steroidal-anti-inflammatory-drugs-and-diclofenac-reviews
[25] Clarke, G. D., Adams, I. M., & Dunagan, F. M. (2008). Using suitability profiles to better inform consumers' choice of commonly used over-the-counter analgesics. *International Journal of Pharmacy Practice*, *16*(5), 333-336.

related adverse effects as per the combined maximum estimation of poor/ultra-metabolisers of codeine cited in the Interim Decision.[26]

If codeine is completely removed from Schedule 3, a significant proportion of patients who are currently taking paracetamol/codeine combination products would not be able to treat their condition with a combination product containing an NSAID, hence they will have little choice but to obtain a prescription medicine analgesic. A Guild consumer survey conducted in April 2015 mentioned in the pre-meeting submission, found 59 per cent of respondents were taking some form of paracetamol/codeine combination.

The toxicity of a substance[27]

The Interim Decision makes several references to risk of ultra-rapid and poor metabolisers of codeine. The decision states:

> *The major impact on public health of the proposed amendment would be a reduction in the risk to those individuals who, unbeknownst to themselves, have a rapid metaboliser phenotype of CYP4502D6 and are therefore at significant risk of excessive morphine concentrations following ingestion of usually recommended doses of codeine for any indication.[28]*

In this context, the Guild believes that the risks of harm to a very small number of individuals (some studies have put the number of ultra-metabolisers at 3 per cent of the population[29]) needs to be balanced against of the vast majority of patients who use these products safely and effectively, particularly given the risk of harm cannot be mitigated purely through rescheduling as noted in the Interim Decision:

> *If codeine is to remain in use as an analgesic, then the patient's metaboliser status needs to be ascertained prior to prescription or dispensing, however this is not practical. [30]*

Taking into account the statement above that it is **not practical** to ascertain a patient's metaboliser status, the Guild queries why this argument is emphasised as a justification for rescheduling, as it will restrict access to the majority of patients who are **not** poor/ultra-metabolisers while offering no additional safeguards for patients who are.

The Guild argues that low dose codeine products should remain in Schedule 3 for the following reasons:

- For patients who are poor metabolisers, the introduction of the real-time monitoring system could enable pharmacists to readily identify patients who may be poor metabolisers based on previous usage contained in the system.

- The Guild wishes to draw attention to a new pharmacy initiative whereby pharmacists and medical practitioners work together so that a patient's CYP2D6 status can readily be obtained. Further information can be found in **Attachment 2**.

- For ultra-metabolisers who are unavoidably exposed to codeine, the Guild considers that it would be worse in terms of adverse events if these patients used a prescription medicine with a higher dose of codeine rather than a low dose product.

[26] Interim decisions & reasons for decisions by delegates of the Secretary to the Department of Health – October 2015, 16
[27] Section 52E(1b)- *Therapeutic Goods Act 1989*
[28] Interim decisions & reasons for decisions by delegates of the Secretary to the Department of Health – October 2015, 13-14
[29] See Attachment 2, 4
[30] Interim decisions & reasons for decisions by delegates of the Secretary to the Department of Health – October 2015, 17

The potential for abuse of a substance[31]

Addressing abuse/misuse through rescheduling

There has been ongoing discussion regarding the potential and actual rate of misuse/abuse of codeine. OTC codeine medicine abuse is a recognised problem internationally but is not completely understood. Studies have indicated research is needed to quantify the scale of abuse, evaluate interventions and capture individual experiences, to inform policy, regulation and interventions.[32]

The Guild believes it is often difficult to draw meaningful conclusions from reports due to factors such as:

- The dates that are covered as part of the study. Many studies assess abuse/misuse of codeine prior to 2010, when OTC codeine was rescheduled from Schedule 2 to Schedule 3 and the maximum available pack size was greatly reduced. Therefore, any conclusions made on OTC codeine based on data pre-2010 are not factoring in critical changes to the scheduling of these medicines.

- Lack of specificity of misuse/abuse for OTC codeine compared to prescription codeine products. Several studies suggest that abuse/misuse of prescription codeine products is similar or worse than OTC codeine.[33] Therefore the effectiveness of rescheduling codeine to prescription to address abuse/misuse must be questioned.

- Additional factors involved in abuse/misuse such as multiple drug toxicity and high rates of comorbid health problems such as mental illness illicit substance use and chronic pain.[34]

Accurately estimating the associated risk for the general population is difficult, which the NDPSC noted when it considered the scheduling of codeine in 2009. As noted in the Interim Decision, while the NDPSC stated it was not possible to accurately estimate the associated risk of harm, it was reasonably assumed:

- The proportion of all users abuse OTC CCA is low
- The risk of harm among all users of OTC CCA is low
- The risk of harm among abusers of OTC CCA is high.[35]

In spite of this, the Interim Decision states the following:

> *Rescheduling to Schedule 3 has not achieved the required reduction in harm to affected individuals. Since the rescheduling of codeine in 2010 there hasn't been the reduction that might have occurred.*[36]

The Guild questions the evidence behind this assertion, particularly as the NDPSC did not provide definitive figures of abuse/misuse in 2009. It is also not clear what the term "required reduction" means in the context.

The Guild also notes that industry specific data indicates that in the three years immediately following the rescheduling of codeine products from Schedule 2 to Schedule 3 in 2010, there was a 12 per cent decline

[31] Section 52E(1e)- *Therapeutic Goods Act 1989*
[32] Cooper, R. J. (2013). Over-the-counter medicine abuse–a review of the literature. *Journal of substance use*, *18*(2), 82-107.
[33] Roxburgh, A., Hall, W. D., Burns, L., Pilgrim, J., Saar, E., Nielsen, S., & Degenhardt, L. (2015). Trends and characteristics of accidental and intentional codeine overdose deaths in Australia. *The Medical journal of Australia*, *203*(7), 299-299.
[34] Roxburgh, A et al. (2015). Trends and characteristics of accidental and intentional codeine overdose deaths in Australia.
[35] Interim decisions & reasons for decisions by delegates of the Secretary to the Department of Health – October 2015, 14
[36] IBID, 15

in OTC codeine medicines sales in terms of units sold.[37] This is in contrast to an increase in pain medications dispensed on the PBS over the same period as shown in the table below.

Substance	Increase in volume sales (2010-2013) [38]
Prescription codeine	3 per cent
Tramadol	3 per cent
Oxycodone	15 per cent

While the rescheduling of codeine from Schedule 2 to Schedule 3 has had an impact (demonstrating the role pharmacists play in determining the therapeutic need for Pharmacist Only products), the rapid increase in volume and misuse/abuse of prescriptions opioids such as oxycodone demonstrates scheduling alone cannot be expected to fully address misuse and abuse.

Rescheduling appears to be a blunt instrument to manage abuse/misuse. As mentioned in our pre-meeting submission, there are more effective measures where combined with the introduction of a real-time monitoring system that are likely to more effective in addressing abuse/misuse without restricting access to the majority of patients who use these products safely and effectively, these include:

- Mandatory warning labels advising consumers of the potential for dependence from prolonged use of these products (greater than 3 days);
- Ongoing education for pharmacists;
- Consumer awareness campaign (further information provided under Additional Matters that the secretary considers necessary to protect public health).

Scheduling Policy Framework

The following comments are made in the Interim Decision:

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

Codeine in Schedule 3 products are only indicated for the treatment of acute pain and are sold in small packs (maximum 5 days' supply). Studies show that dependence is associated with the regular/prolonged use of codeine usually related to the treatment of chronic pain conditions.[39] [40] Studies conducted in Australia indicate that patients who are susceptible to codeine dependency are more likely to have taken well above the recommended doses of OTC codeine and have taken it for considerably longer periods of time than recommended.[41]

Cases examining morbidity associated with misuse of over-the-counter codeine-ibuprofen analgesics indicated that patients were taking mean daily doses of 435-602 mg of codeine phosphate and 6800-9400

[37] Nielsen Pharmacy Scan, Jan 2010 – May 2013
[38] PBS expenditure and prescriptions www.pbs.gov.au/info/browse/statistics#Expenditure . These figures do not account for medicines dispensed as a private script over this period.
[39] Sproule, B. A., Busto, U. E., Somer, G., Romach, M. K., & Sellers, E. M. (1999). Characteristics of dependent and nondependent regular users of codeine. *Journal of Clinical Psychopharmacology*, *19*(4), 367-372.
[40] Ford, C., & Good, B. (2007). Dependence on OTC drugs: Over the counter drugs can be highly addictive. *BMJ: British Medical Journal*, *334*(7600), 917.
[41] Nielsen, S., J. Cameron, and N. Lee. "Characteristics of a non-treatment-seeking sample of over-the-counter codeine users: implications for intervention and prevention." *Journal of opioid management* 7.5 (2010): 363-370.

mg ibuprofen. These amounts are greatly in excess of what a patient can obtain in a single pack of Schedule 3 codeine product and the stipulated maximum daily dose of 100mg of codeine that must be included as part of the labelling.[42]

The evidence suggests taking Schedule 3 codeine medicines, when used as directed to treat episodic pain at the maximum daily dose and maximum treatment period has little risk of producing dependency. This reflects previous statements made by the NDPSC in 2009 that stated the proportion of all users who abuse OTC CACC and the risk of harm among all users of OTC CACC is low. It is when patients exceed the recommended daily doses and/or prolong their use beyond what is recommended the risk is evident.

Therefore the Guild believes a Schedule 3 listing for CCAs is consistent with the SPF.

In order to ensure patients do not obtain codeine products in quantities that are likely to produce dependency, a real-time monitoring system needs to be implemented so that pharmacies can determine where and when patients have previously purchased Schedule 3 codeine products and therefore make a fully informed determination regarding the therapeutic need for a product.

Rescheduling these products to Schedule 4 will simply shift the problem to medical practitioners who will have the same difficulty in determining whether a patients' previous and current use is consistent with therapeutic guidelines.

Any other matters that the Secretary considers necessary to protect public health[43]

Overseas classifications of codeine

The Interim Decision makes the following statements in relation to the available of codeine in other countries:

> *In Europe codeine is not an OTC medicine (i.e. is a prescription only medicine at least) in 13 countries being Austria, Belgium, Croatia, the Czech Republic, Finland, Germany, Greece, Italy, Luxembourg, Portugal, Slovakia, Spain and Sweden.*
>
> *Codeine is also a Prescription Medicine in the USA, Hong Kong, Iceland, India, Japan, the Maldives, Romania, Russia, and the United Arab Emirates.* [44]

The Guild cautions against making direct comparisons regarding the availability of codeine in other countries given the significant differences in the scheduling systems. For example, the Unites States does not have any OTC schedules meaning all non-prescription medicines can be sold in a non-pharmacy setting with no controls over supply. As a result, there are several medicines that are available OTC in Australia that require a prescription in the Unites States.

There are also many other countries where low dose codeine products are available OTC and are classified as Pharmacy Medicines. These include:

- United Kingdom – All codeine products must have mandatory labelling warning of the potential for addiction. In addition, pack size is limited to three days' supply.
- New Zealand (the country whose scheduling system most closely resembles Australia)

[42] Poisons Standard July 2015 – Schedule 3 listing codeine www.comlaw.gov.au/Details/F2015L00844
[43] Section 52E(1f)- *Therapeutic Goods Act 1989*
[44] Interim decisions & reasons for decisions by delegates of the Secretary to the Department of Health – October 2015, 14

- Canada
- Denmark
- France
- Ireland
- South Africa – have a real-time monitoring system

Consumer Awareness Campaign

There is a lack of awareness within the Australian public that *Pharmacist Only* Medicines are not available for purchase without a pharmacist's assessment for appropriateness and safety. The Guild are working with the consumer groups and other relevant stakeholders in this regard. To complement this, the Guild are supporting pharmacists with their professional obligations in managing requests and recommendations for CCAs and other *Pharmacist Only* Medicines.

Additional impacts of scheduling decision

The Guild notes the following comment made in the Interim Decision:

> *Potential unintended consequences and disadvantages of a decision to reschedule CCAs to S4 need to be considered. One would be a reduction in the availability of analgesics for moderate to severe pain, although the evidence suggests that the addition of codeine adds only a minor additional analgesic effect over and above that of the ibuprofen or paracetamol in the combination product. The recent introduction of a paracetamol/ibuprofen combination may fill this niche more effectively than the CCAs have done, without the disadvantages of codeine. A reduction in the availability of a drug known as an anti-tussive agent, despite the lack of evidence available to support this, would also occur, but significant actual disadvantages are unlikely to occur. No other potential disadvantages to the community are readily identified.*[45]

The Guild has already highlighted problems with the statements made in the Interim Decision regarding combination ibuprofen/paracetamol products are alternatives for all patients. The Guild has also noted evidence in relation to the efficacy of low-dose CCAs over single ingredient analgesics.

In addition, the Guild does not believe the full consequences and disadvantages of this scheduling decision have been properly considered. Several potential unintended consequences that must be formally considered include:

- The decision to reschedule codeine will add significant costs to the MBS and PBS as well as patient's out of pocket expense;

- For patients who do not have easy and/or affordable access to a prescriber in their local area, their pain management is likely to suffer. This is likely to be a significant factor in rural/remote areas. This in turn may result in:
    - An increase in presentations to emergency departments, which increase health costs for State/Territory Governments; and
    - Patients self-medicating with non-therapeutic products such as alcohol or illicit substances.
- The scheduling changes will require many sponsor companies to reformulate their products to remove the codeine if they wish to keep supplying the product as an OTC product. The process of reformulation and re-registering the product with the TGA will likely extend well beyond the current proposed implementation date of June 2016. Alternatively, some products may be discontinued meaning the products will no longer be available in any schedule. This could result

[45] Interim decisions & reasons for decisions by delegates of the Secretary to the Department of Health – October 2015, 14

in a shortage of cold and flu products for the start of the 2016 winter season. This could also lead to further demand on emergency hospital services.

Furthermore, many medical practices (particularly practices in rural/remote and lower socioeconomic areas) have limited additional capacity to see more patients, hence it will be challenging for these practices to accommodate the likely substantial increase in visitors to obtain prescriptions for codeine. This will likely result in reduced availability of medical practitioner services and an increase in waiting time for all patients. Patients who reside in regional, rural and remote areas would be most impacted, given the time and cost to visit a medical practitioner is substantially greater compared to metropolitan areas.[46]

Given the sheer magnitude and extent the proposed scheduling amendment will cause to a wide range of stakeholders, the Guild believes it is imperative that a formal regulatory impact statement (RIS) be conducted prior to any decision on rescheduling. This RIS should also examine the comparative risk/benefits of implementing a national real-time monitoring system as an alternative strategy.

Recommendation

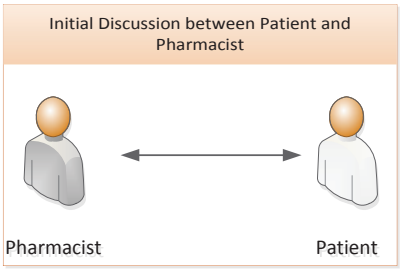
The Guild believes that given the widespread implications and cost of the rescheduling proposal, it is imperative that a formal regulatory impact statement (RIS) be conducted prior to any decision on rescheduling. This RIS should also examine the comparative risk/benefits of implementing a national real-time monitoring system as an alternative strategy

[46] National Health Performance Authority Media Release 01 October 2015 – People 2 to 3 times more likely to avoid seeing a GP die to cost in some areas

High Level Workflow for recording S2/S3 medicines

Version 0.2

Step 1: Patient and Pharmacist Initial Discussion



Is a Codeine based product requested or recommended?

NO → Step2: S2/S3 Recording Solution Prototype not required

YES

Step 2: S2/S3 Recording Solution Prototype workflow

START: Select Initial Discussion checkbox

Select Purchase Initiated By

Photo ID presented

Prompt for Patient Consent

Consent Granted?

NO → START

YES

Product located and selected

Display the Transaction/Product Request history for Photo ID entered

Continue?

NO → **Purchase is Denied?**

YES → Record Reason and Finish

NO → Select Safety Sale or Cancelled and Finish

YES

Present Decision Support Questions

Allow Purchase?

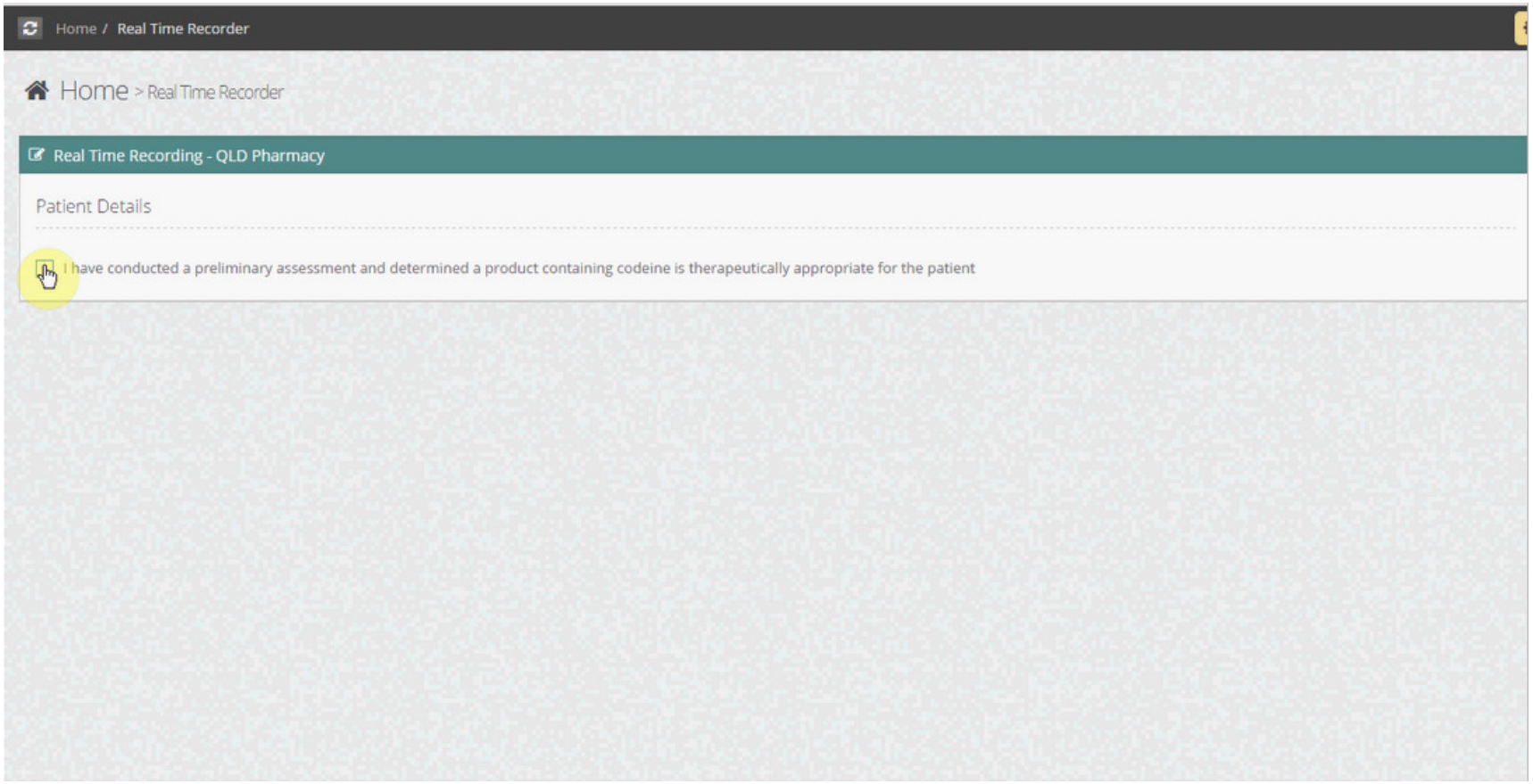
NO

YES

Finish

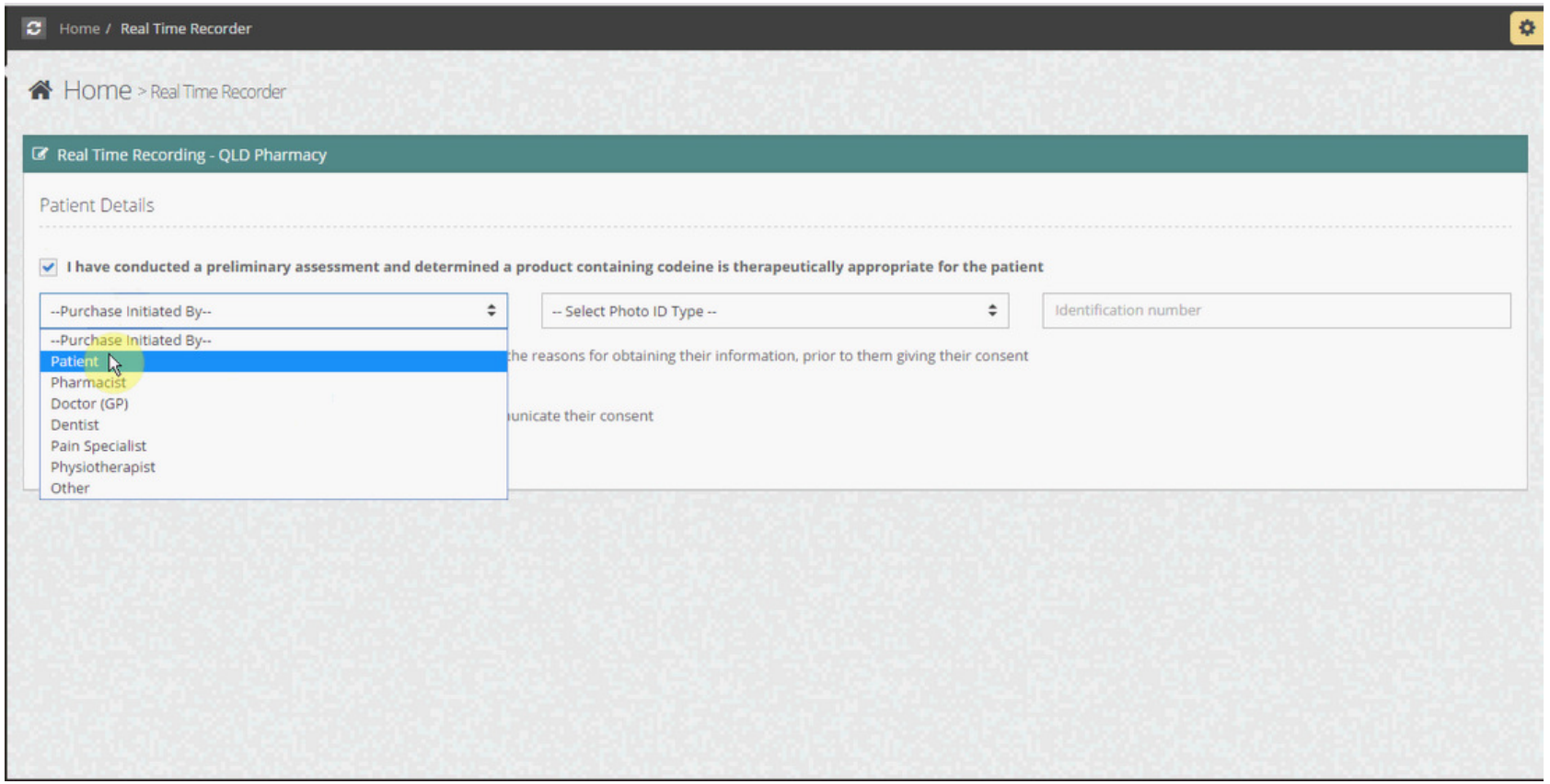
- **Green** indicates the workflow if the answer to the question is Yes
- **Blue** indicates the workflow if the answer to the question is No
- **Red** indicates the decision points throughout the workflow

Screen Shots of Real-time Monitoring System



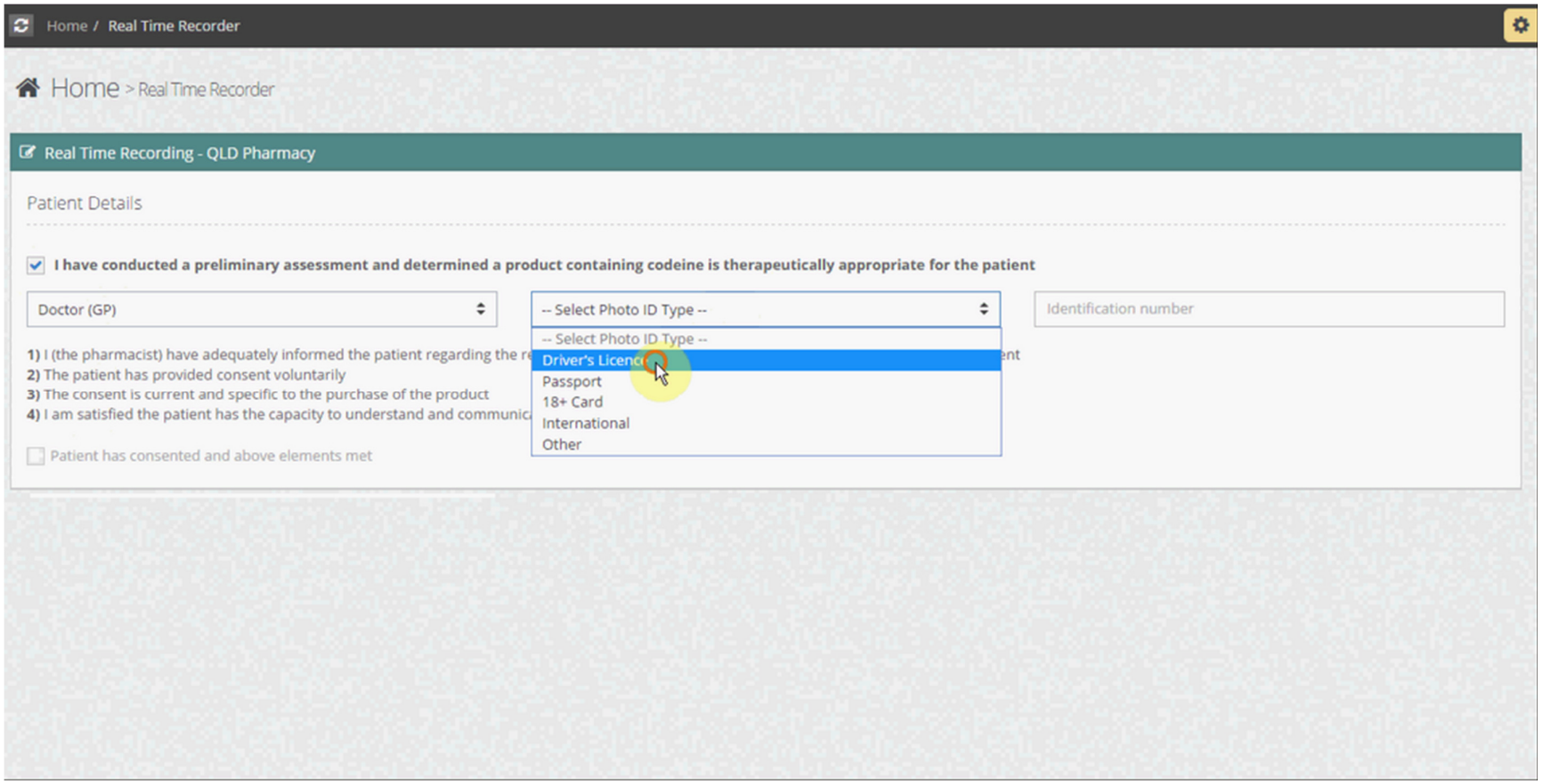
Screenshot 1 of 15 – Preliminary assessment conducted

Screen Shots of Real-time Monitoring System



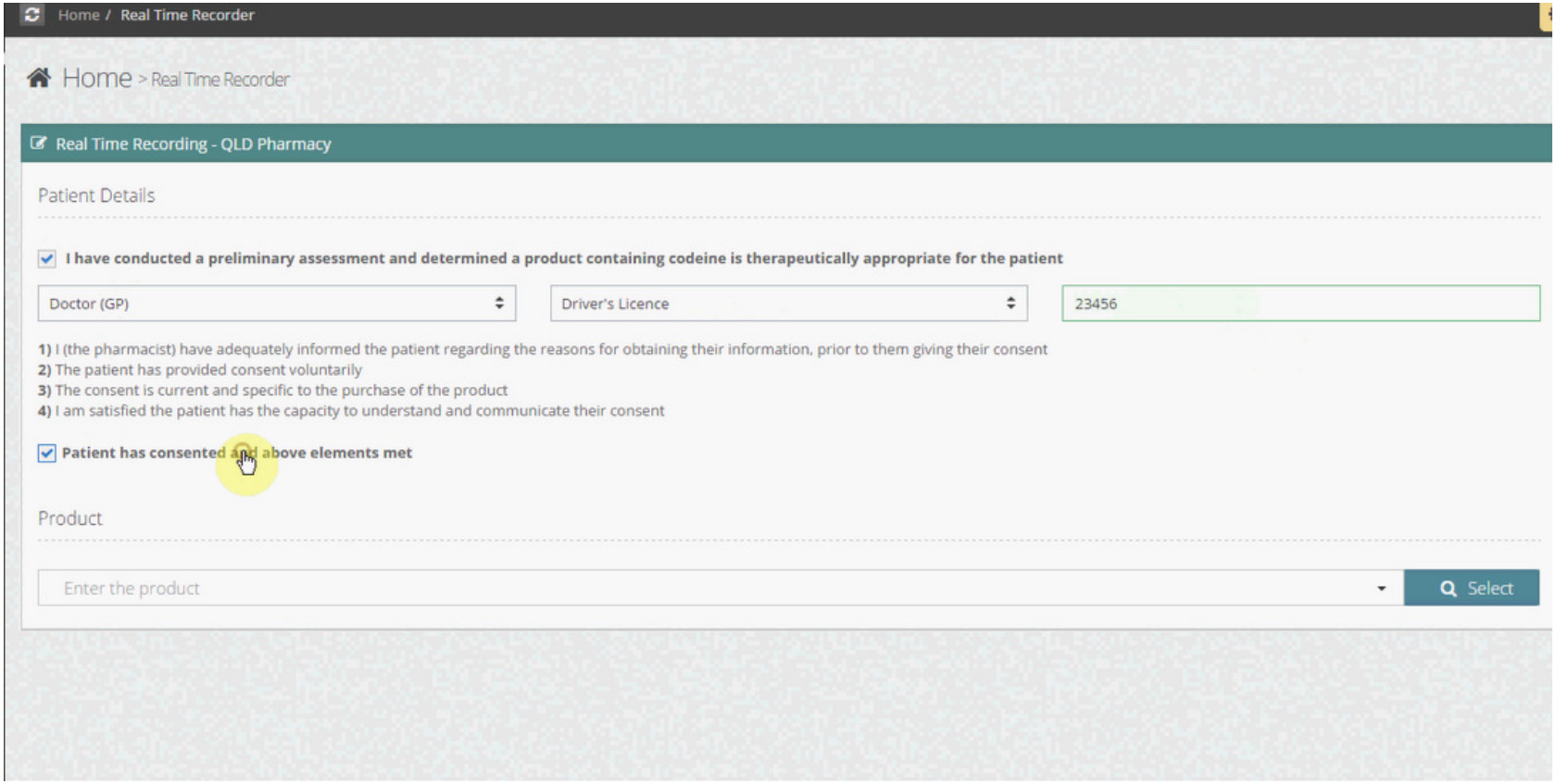
Screenshot 2 of 15 – Purchase initiated by

Screen Shots of Real-time Monitoring System



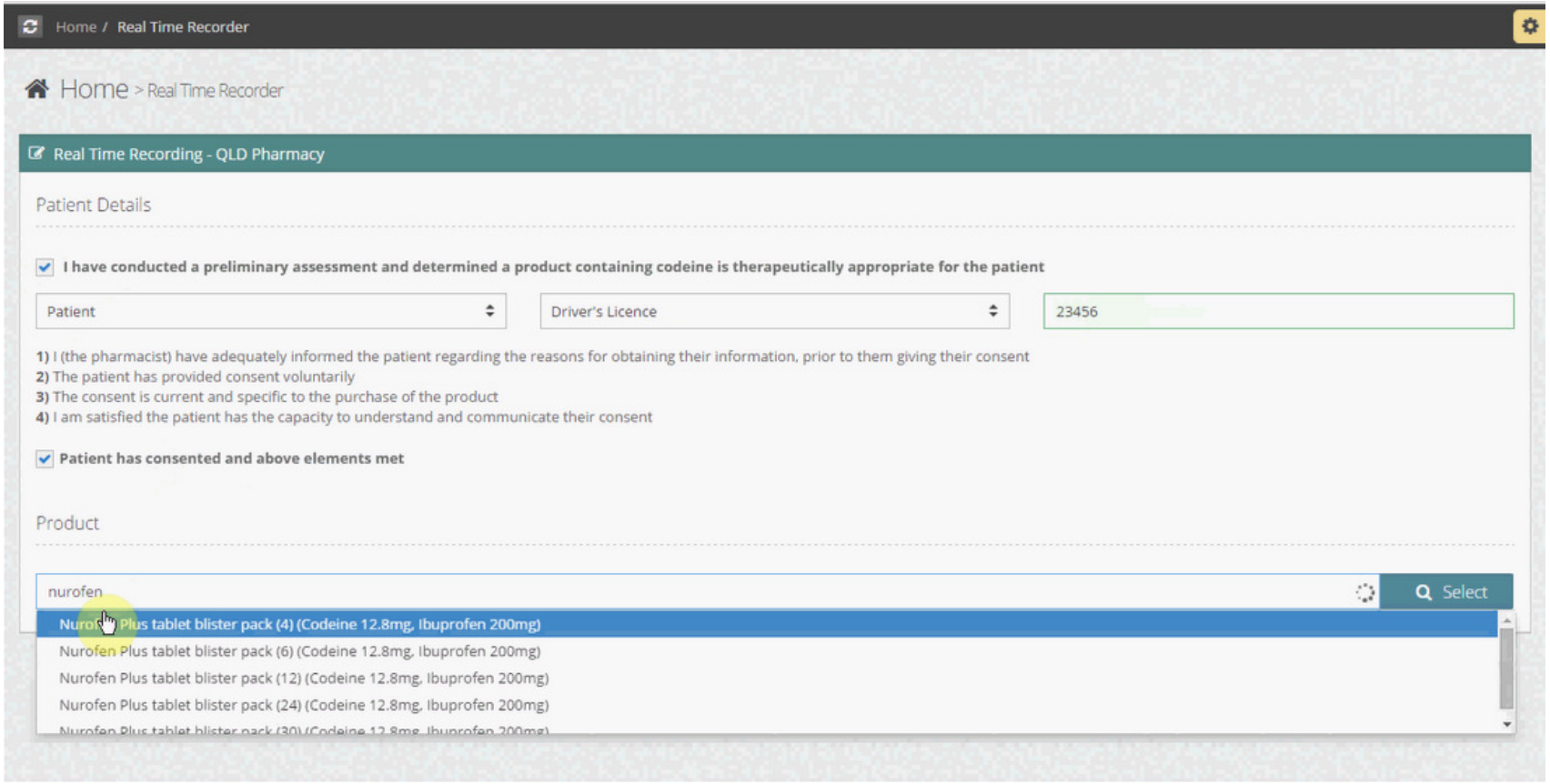
Screenshot 3 of 15 – Select Photo ID

Screen Shots of Real-time Monitoring System



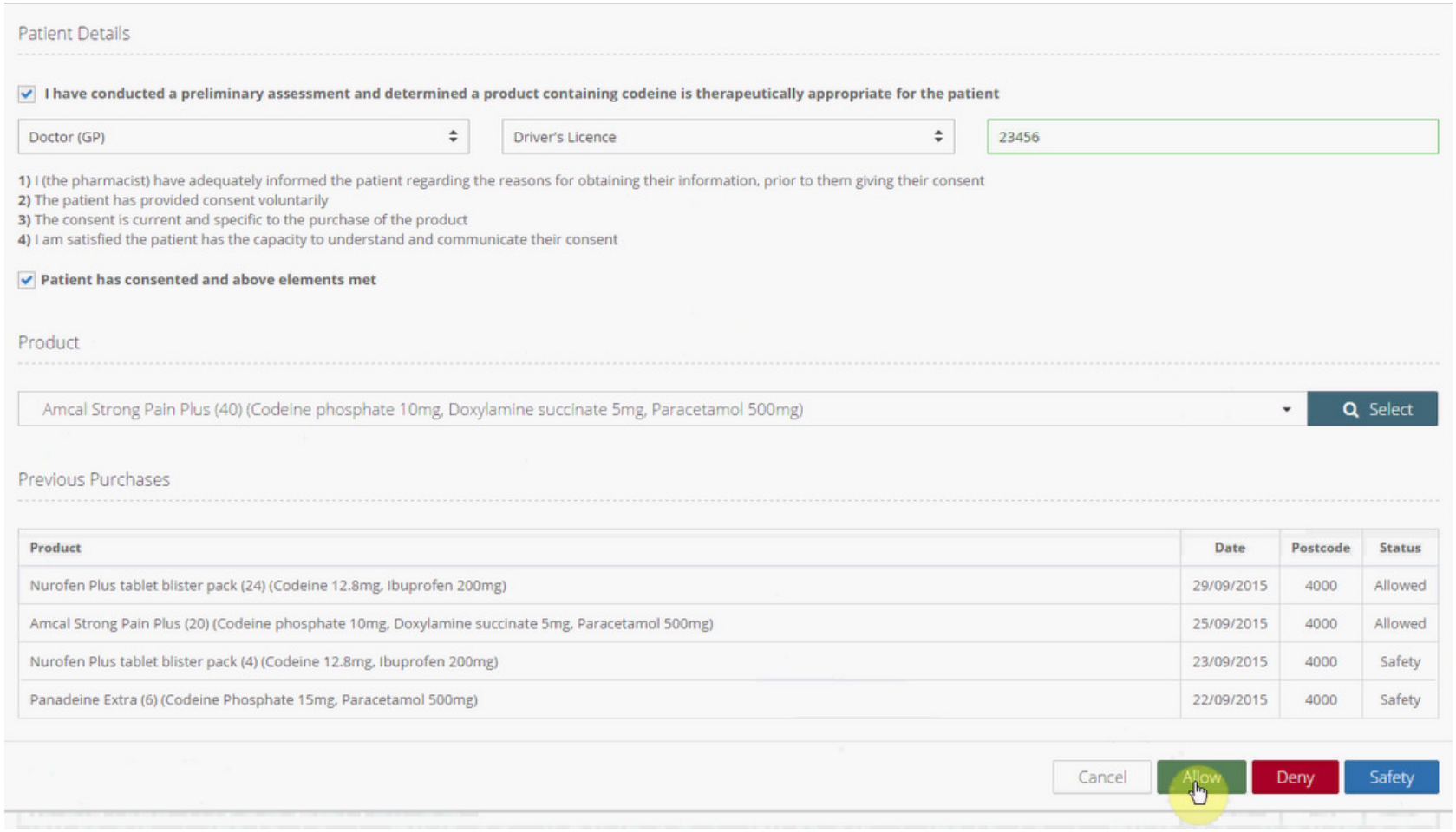
Screenshot 4 of 15 – Patient consent obtained

Screen Shots of Real-time Monitoring System



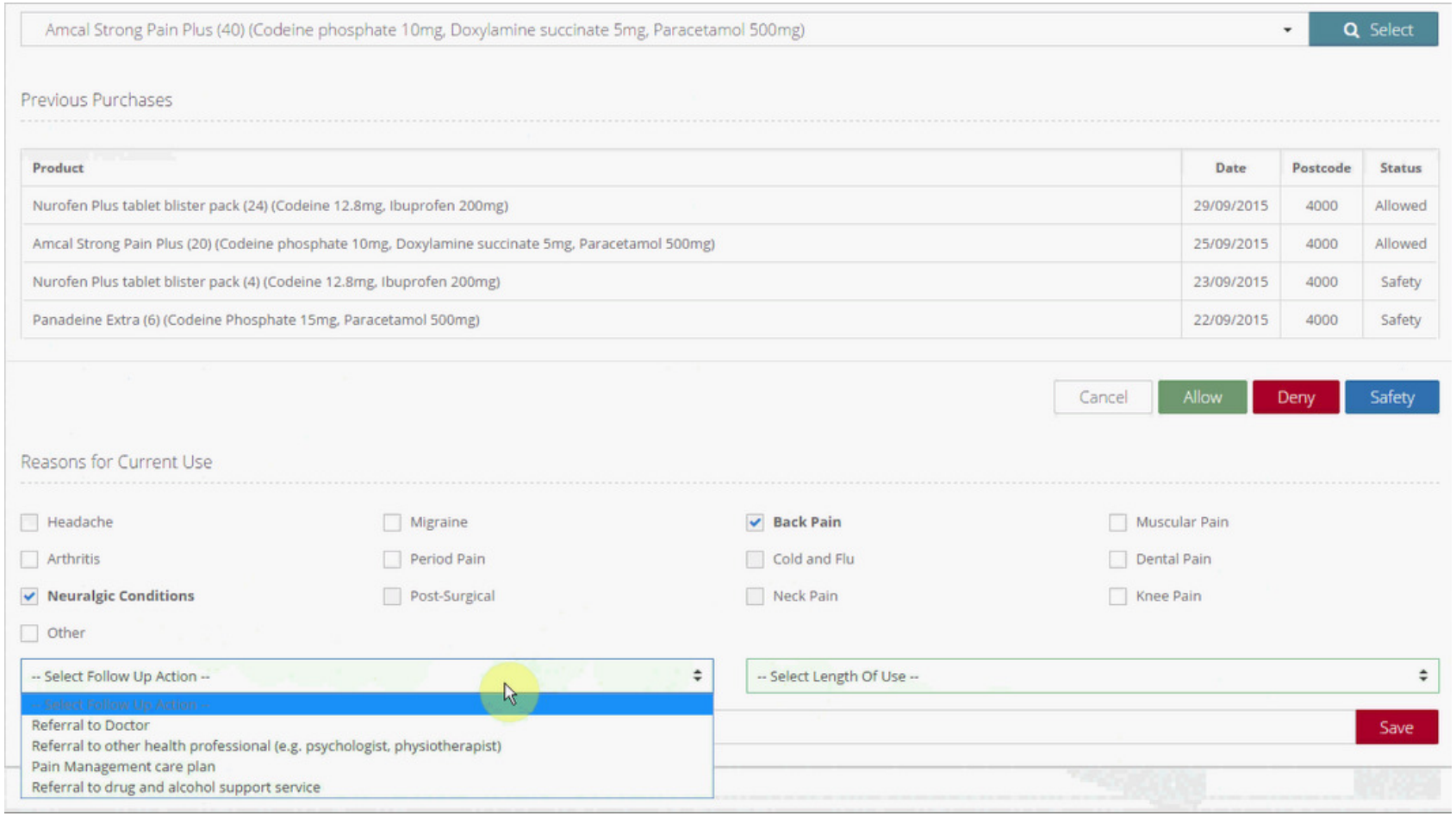
Screenshot 5 of 15 – Product name entered

Screen Shots of Real-time Monitoring System



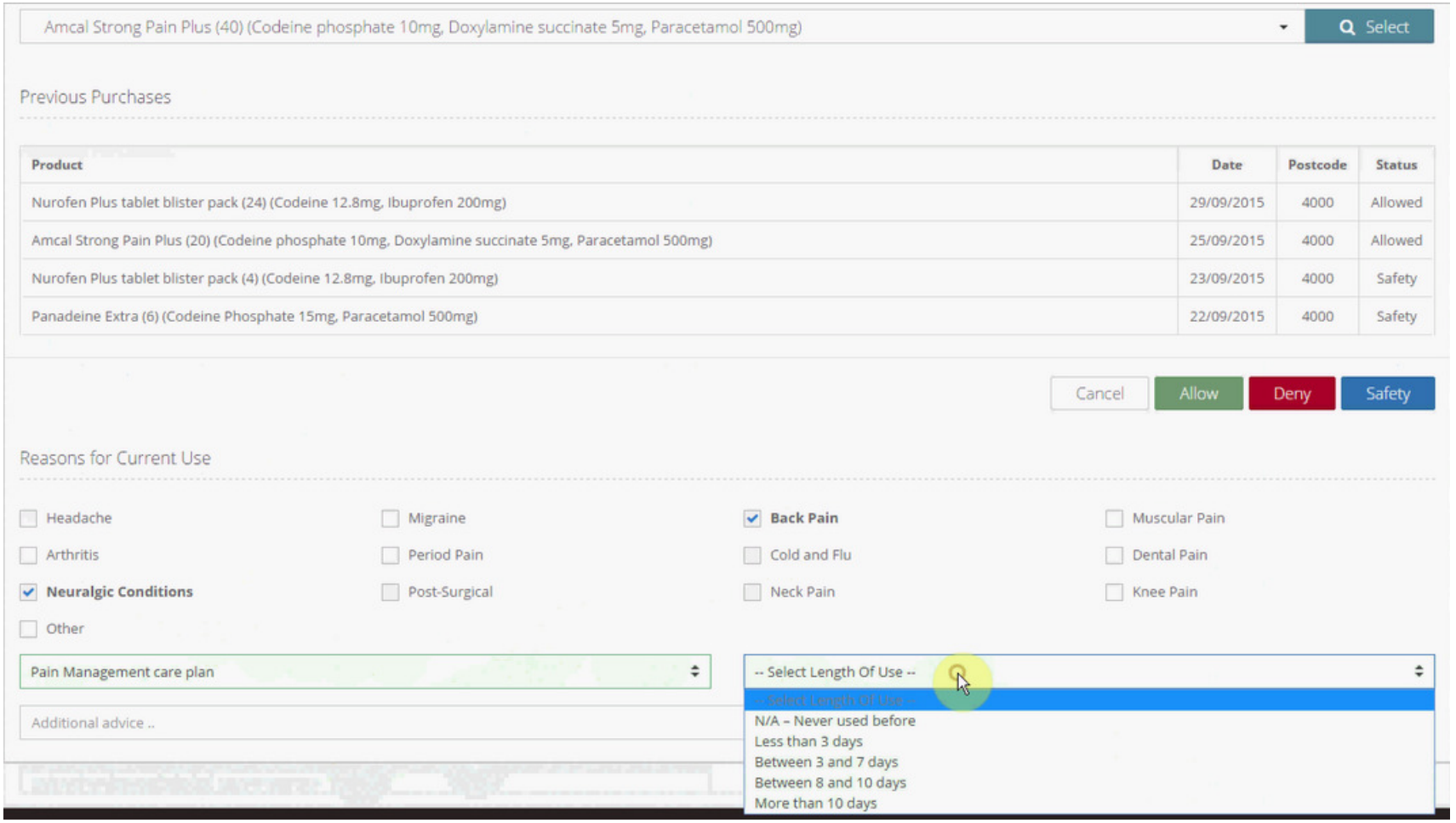
Screenshot 6 of 15 – Previous History viewed and sale allowed

Screen Shots of Real-time Monitoring System



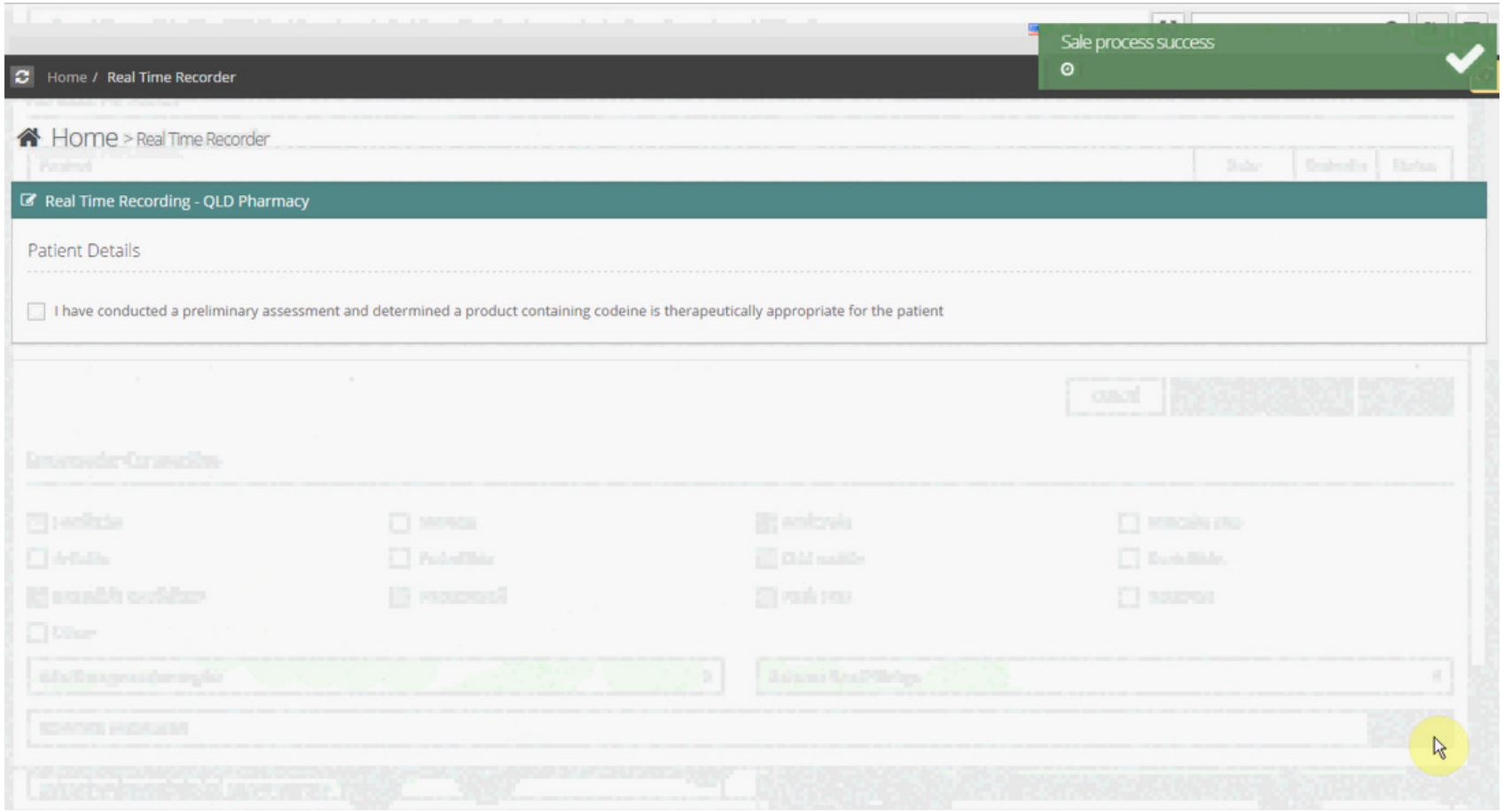
Screenshot 7 of 15 – Reason for current use and follow action up recorded

Screen Shots of Real-time Monitoring System



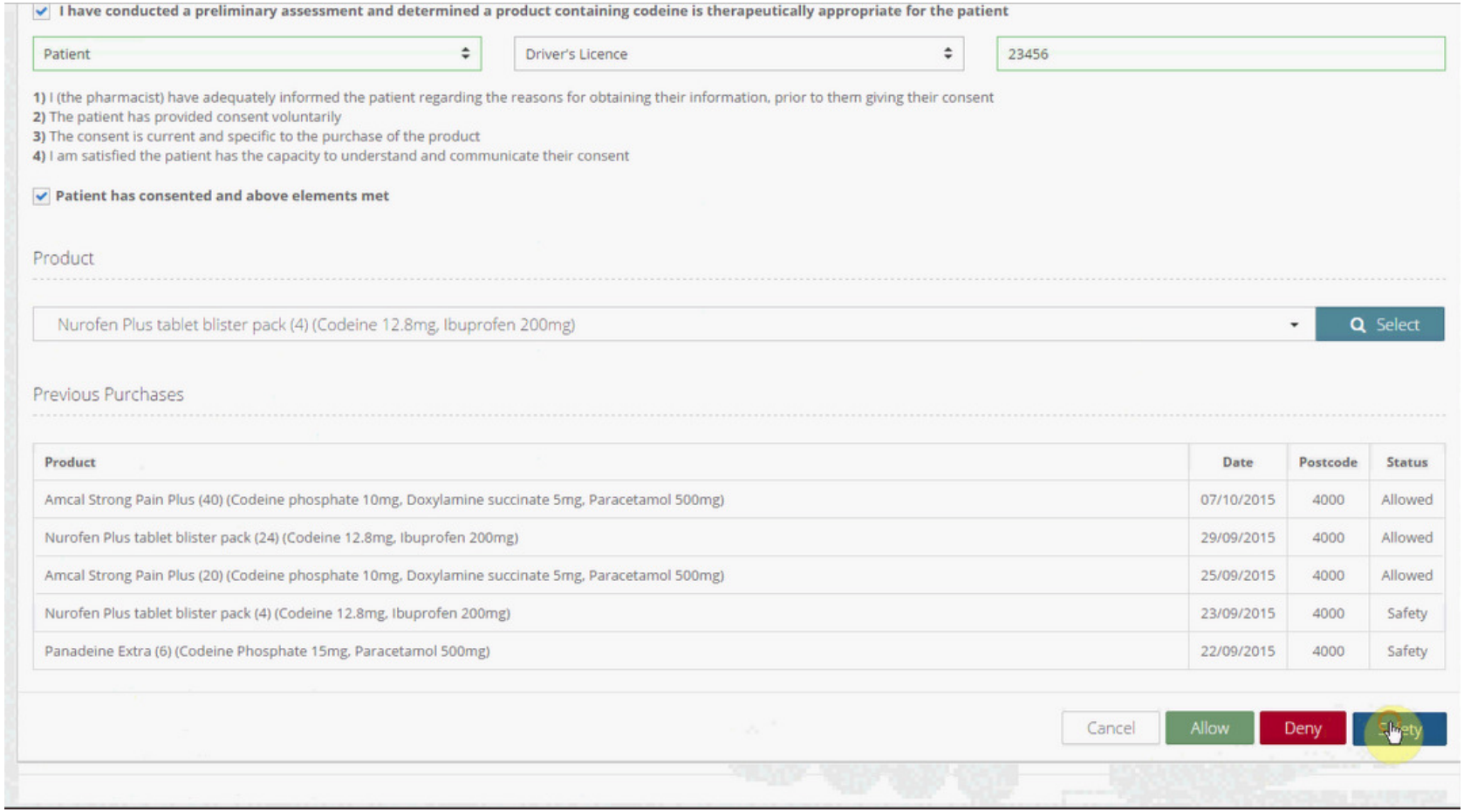
Screenshot 8 of 15 – Length of use and additional advice (free text)

Screen Shots of Real-time Monitoring System



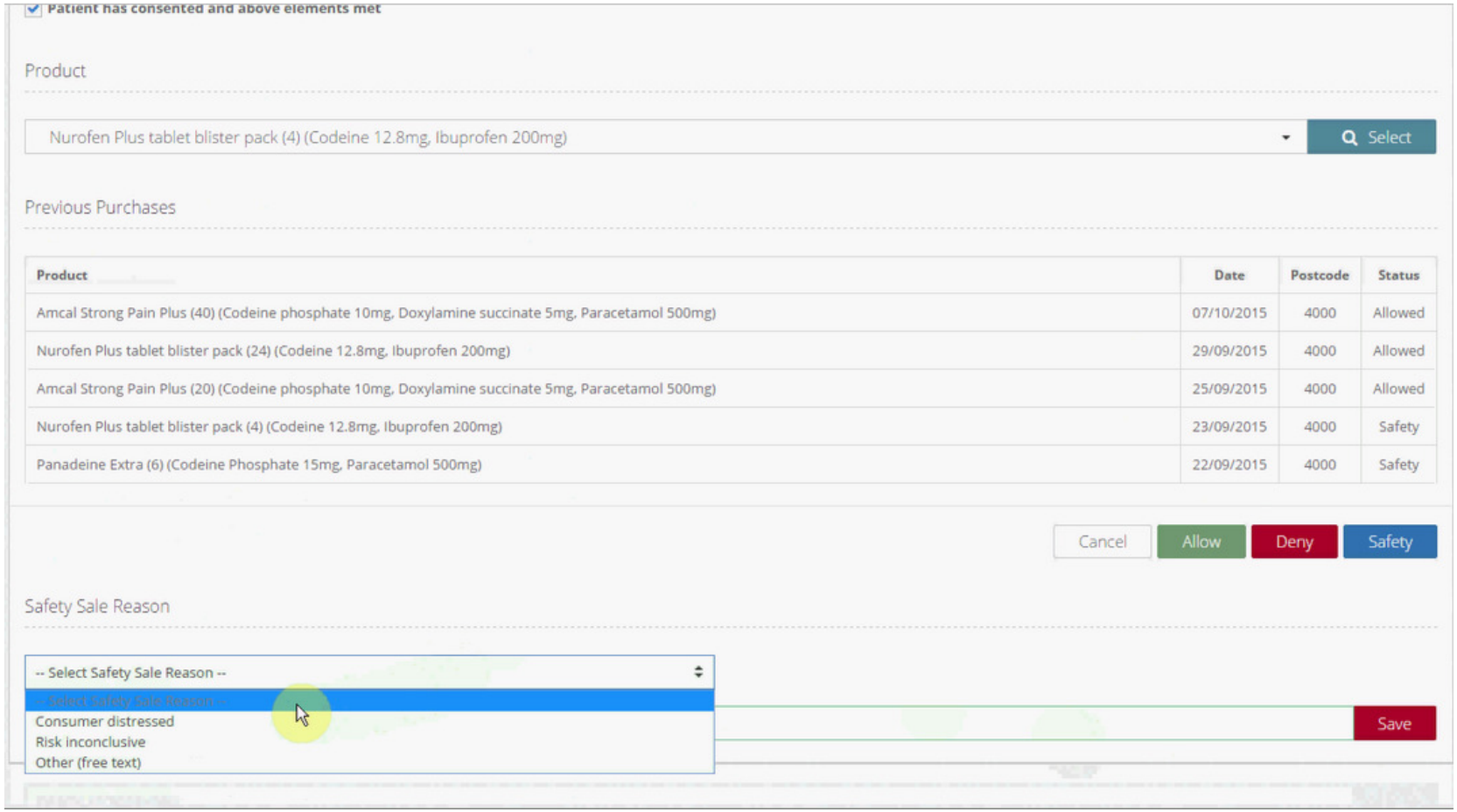
Screenshot 9 of 15 – Sale process complete and record saved

Screen Shots of Real-time Monitoring System



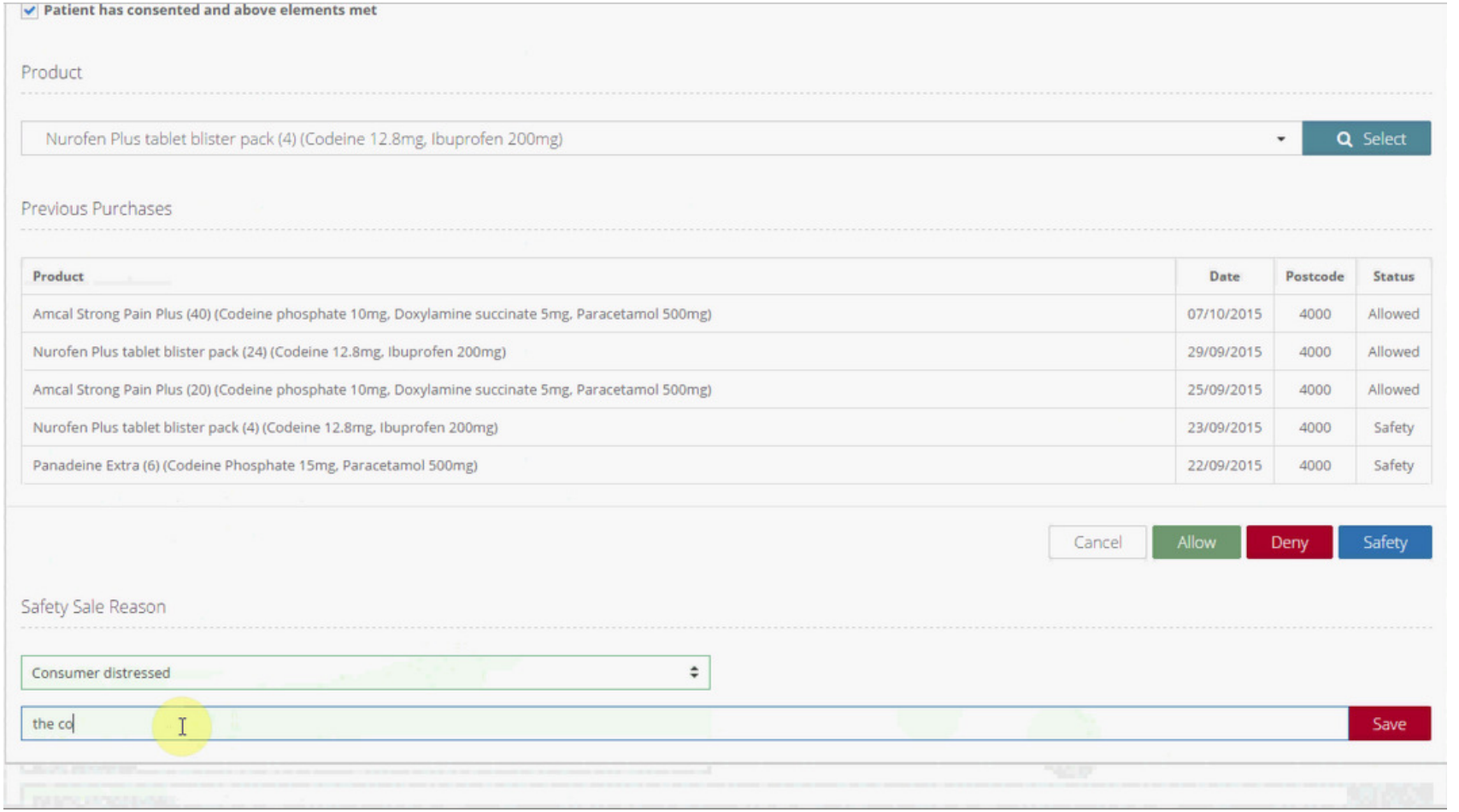
Screenshot 10 of 15 – Safety Sale

Screen Shots of Real-time Monitoring System



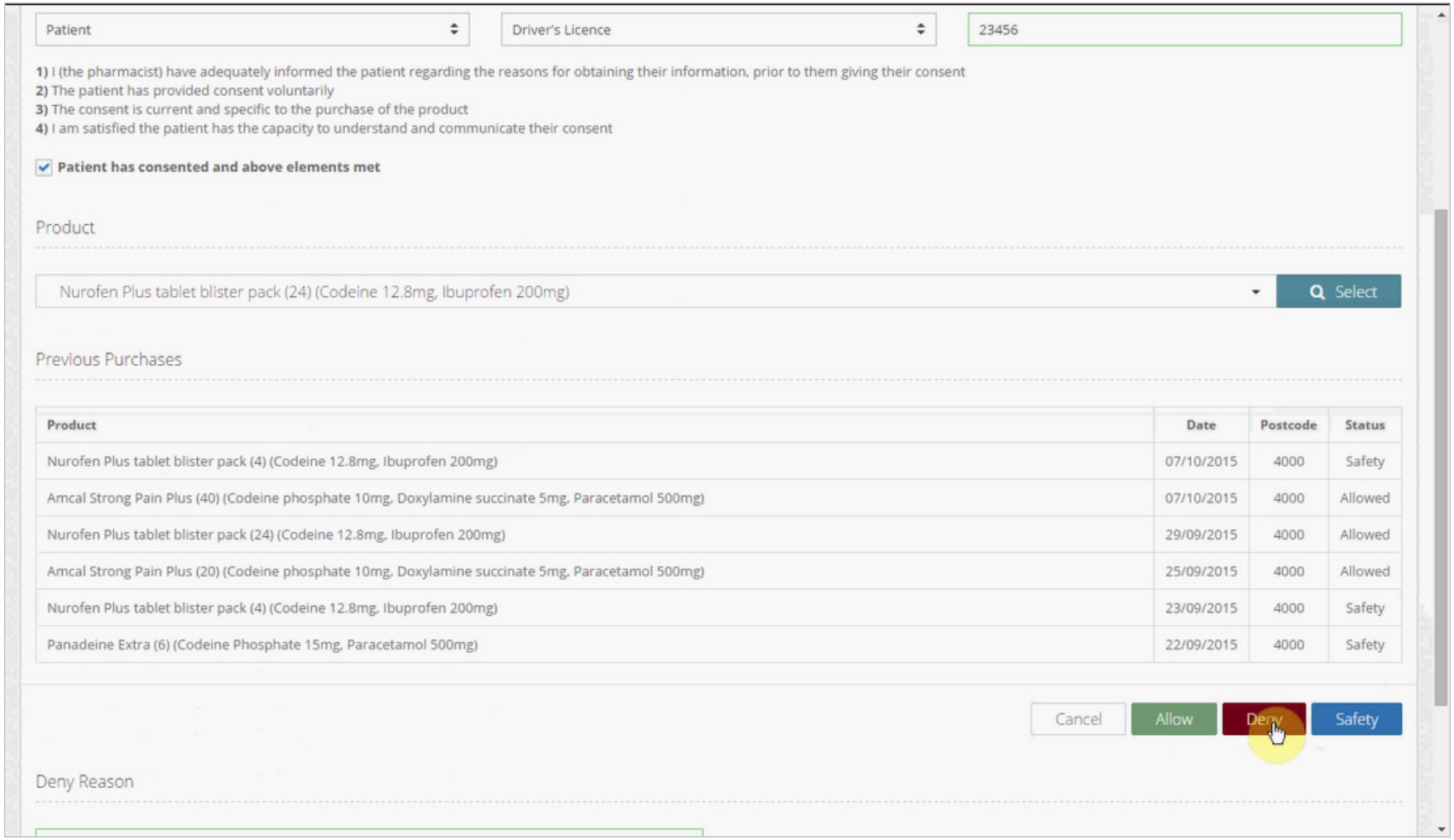
Screenshot 11 of 15 – Safety Sale Reason

Screen Shots of Real-time Monitoring System



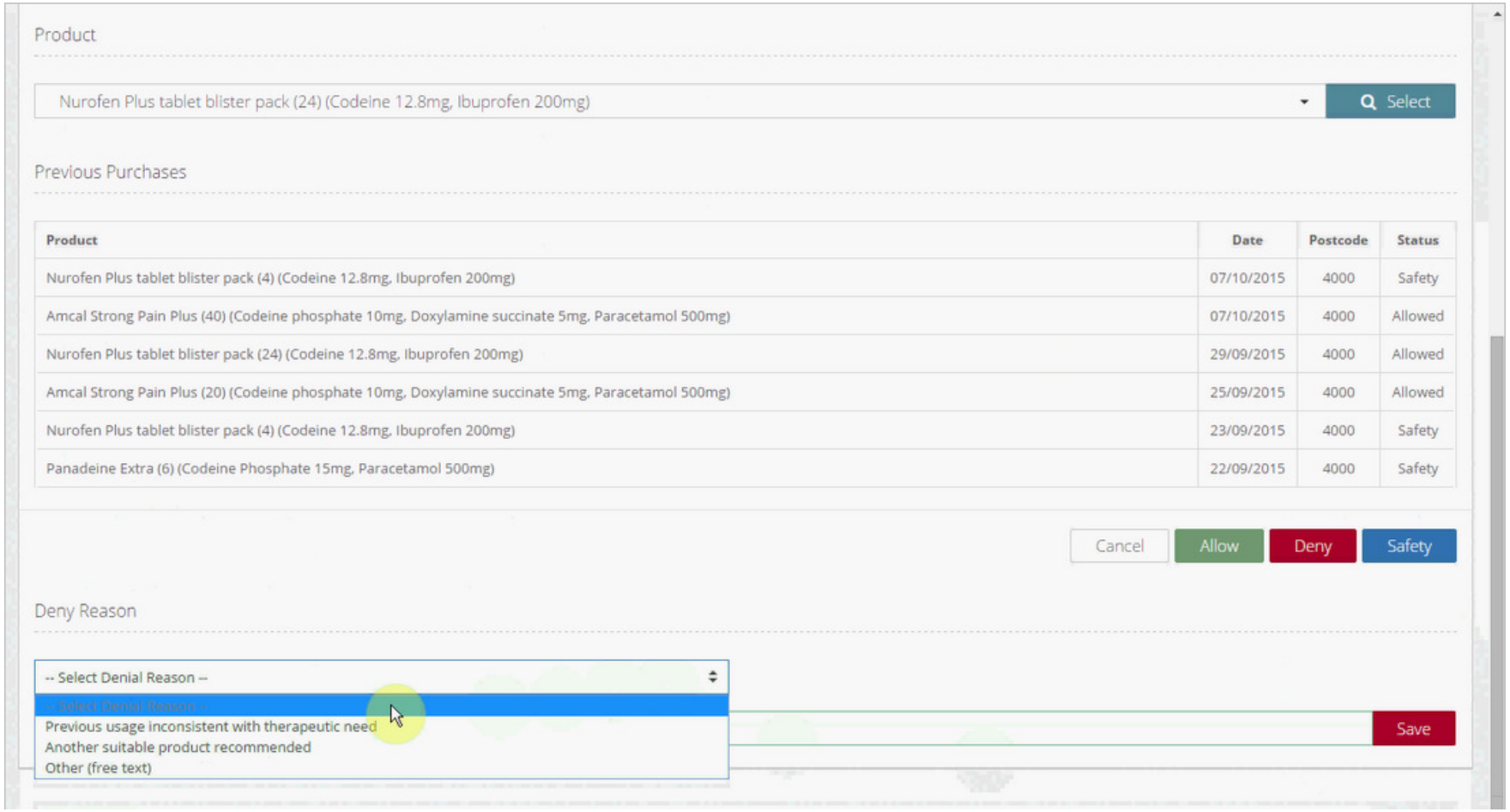
Screenshot 12 of 15 – Additional information recorded (Free Text)

Screen Shots of Real-time Monitoring System



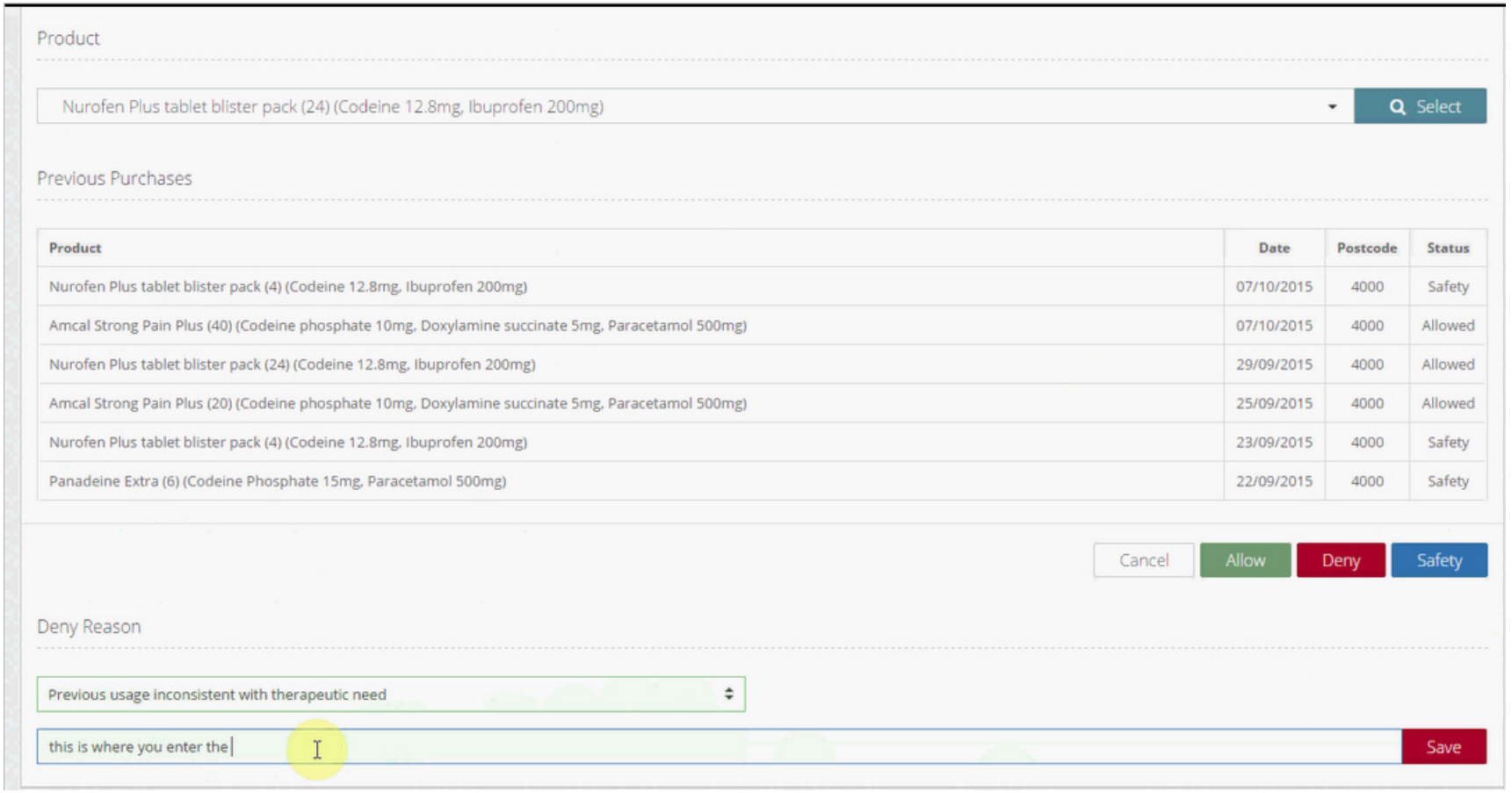
Screenshot 13 of 15 – Sale Denied

Screen Shots of Real-time Monitoring System



Screenshot 14 of 15 – Reason for sale denied

Screen Shots of Real-time Monitoring System



Screenshot 15 of 15 – Deny Sale Additional Advice (Free Text)

Pharmacy-based CYP2D6 testing as an alternative to the rescheduling of codeine-containing products

Executive Summary

This submission is a response to the proposed rescheduling of certain codeine-containing items from schedule 3 to schedule 4. The reasons for the Delegate's interim decision listed on pages 12 to 17 include the risk of codeine toxicity – including respiratory depression – and the risk of addiction.

Relevantly, the Delegate notes the significant variability in codeine response as the result of genetic variation in the CYP2D6 enzyme and the risks associated with 'ultrarapid' metabolism. In particular, point 4 on page 14 indicates that 'individuals rarely know their metaboliser status, and testing is not readily available'. The practicality of such testing has also been questioned.

The Pharmacy Guild wishes to draw attention to a new pharmacy initiative whereby pharmacists and medical practitioners work together so that a patient's CYP2D6 status can readily be obtained. Widespread adoption of the program would reduce the need to reschedule codeine as many of the risks associated with its prescription could be accounted for in the pharmacy setting.

The program was recently piloted as a partnership between GenesFx Health (now *My DNA Life)* and several Victorian pharmacies and supported by a grant from Commercialisation Australia. Testing is conducted in the pharmacy setting; however results are communicated to both the pharmacist and a nominated doctor so that both healthcare professionals can maintain active involvement in the process.

After being counseled on the test findings, patients are provided with an 'ID card' that summarises their results so that they can alert future prescribers to their metabolism profile. They are also provided with access to a secure online portal that allows them to check their genetic compatibility with a range of medications in addition to codeine.

To date, over 600 such tests have been conducted across 6 different pharmacies and 300 new doctors have been introduced to pharmacogenomic testing through the program. Analysis of the first 370 results revealed that 52 patients (16%) had been prescribed codeine and 11 patients (3%) had a genetic result predictive of CYP2D6 'ultrarapid' metabolism that places them at an increased risk of codeine toxicity.

Several international bodies regularly review the medical literature and maintain a set of guidelines regarding CYP2D6 genotyping and codeine prescription. The Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends that patients with a genotype predictive of CYP2D6 ultrarapid metabolism should be offered an alternative to codeine. This is largely with view to preventing toxicity. Headline figures in Australia recently

revealed that codeine-related deaths almost doubled between 2000 and 2009. Of the 1400 deaths almost half were accidental overdoses.

It is entirely possible that ultrarapid metabolisers may also be prone to addiction as they are exposed to increased levels of morphine which is produced endogenously from codeine.

In addition, 'poor' and 'intermediate' CYP2D6 metabolisers are unlikely to achieve analgesic effect when taking codeine. The CPIC guidelines recommend avoiding codeine for poor metabolisers and considering alternative analgesics for intermediate metabolisers when no therapeutic response has been achieved. The 370 test results from the pharmacy trial revealed that 65 patients (17.5%) had a genotype predictive of poor or intermediate CYP2D6 metabolism.

Therefore, the pharmacy trial identified approximately 20% of patients as having a CYP2D6 genotype that is likely to limit codeine's effectiveness or expose the individual to a significantly increased risk of toxicity. This proportion is very similar to a larger cohort of 4750 patients who have been tested by *My DNA Life* in preceding years.

It should be noted here that the proportion of CYP2D6 ultrarapid metabolisers is much higher in certain ethnic groups such as East Africans (up to 25%) and Southern Europeans (up to 10%). This further supports the use of CYP2D6 testing given the significant ethnic diversity in the Australian community.

The Victorian trial has demonstrated that pharmacists and medical practitioners can successfully work together to determine a patient's CYP2D6 status and that provision of codeine products can be adjusted accordingly. *My DNA Life* plans to expand this collaborative model throughout Australia so that many more patients can benefit from such testing.

Electronic linkage of pharmacogenomics test results and medication prescribing is already successfully implemented in Holland. A similar initiative to support more widespread testing in Australia would represent an effective way of approaching the problem of codeine toxicity and may be more economical than changing the current codeine scheduling.

1. Pharmacogenomics and Codeine

1.1 Pharmacogenomics

Pharmacogenomics is the study of genetic variations that influence how an individual responds to drugs. It is a central feature of the newly emerging paradigm of 'personalised medicine'. Pharmacogenomic tests are evaluated by studying the strength of the relationship between a particular genetic variable and drug response. When a high level of evidence has been generated, clinical guidelines are created to help doctors use the test in their practice.

Several international bodies regularly review the medical literature and maintain a set of guidelines for clinical use. These include the Clinical Pharmacogenetics Implementation Consortium (CPIC), Canadian Pharmacogenomics Network for Drug Safety (CPNDS) and The Royal Dutch Pharmacists Association - Pharmacogenetics Working Group. Each of these groups has published guidelines for codeine prescription based on genetic testing and these recommendations are based on strong evidence.

1.2 Codeine and CYP2D6

Codeine achieves its analgesic effect via conversion to morphine in the body. The CYP2D6 enzyme is largely responsible for this conversion. The gene encoding the production of CYP2D6 is highly polymorphic – that is, there are many different variations of this gene in the population which influence how efficiently the CYP2D6 enzyme works for an individual patient.

Up to 10% of the population are classified as CYP2D6 'poor' metabolisers due to negligible enzyme function. These people are unlikely to achieve pain relief when taking codeine as they are unable to convert codeine to morphine in their body. A similar proportion of the population are classified as 'intermediate' metabolisers due to significantly reduced CYP2D6 function, and codeine is similarly predicted to be ineffective for these patients.

In contrast, 'ultrarapid' metabolisers have multiple functional copies of the CYP2D6 gene, resulting in very efficient enzyme activity and thus greater conversion of codeine into morphine. These patients are at an increased risk of toxicity due to high morphine blood levels.

There is an extensive body of medical literature that has investigated the relationship between CYP2D6 polymorphisms and codeine response. This literature is summarised in the current CPIC guidelines, however it is worth noting the following key points:

- There are several case reports of fatalities in children taking codeine who have subsequently been identified as CYP2D6 ultrarapid metabolisers;
- Fatalities have also occurred in breasted infants whose mothers are ultrarapid metabolisers taking codeine; and

- These events have resulted in the US Food and Drug Administration (FDA) issuing a boxed warning regarding codeine use in children and breastfeeding mothers.

A summary of the current CPIC guidelines for codeine dosing based on predicted CYP2D6 phenotype is included as an appendix. Further details can be obtained online at the *Pharmacogenomics Knowledgebase*.

1.3 CYP2D6 Genotype Frequencies

Significant variability exists between different ethnic groups with respect to the frequency of CYP2D6 genotypes predictive of poor and ultra-rapid metabolism. A comprehensive literature review conducted by LLerena *et al.* in 2014 summarised the reported frequency of CYP2D6 genotypes and phenotypes across different ethnic groups and geographic regions. The analysis included 44,572 individuals studied in 172 original research papers.

Notably, genotypes predictive of CYP2D6 poor metabolism were reported with a frequency of 8.69% in Scandinavians and genotypes predictive of CYP2D6 ultrarapid metabolism were reported with a frequency of 28.7% in Ethiopians. The following table has been adapted from Table 3 in the original publication.

Continent	Predicted Poor Metabolisers (%)	Predicted Ultrarapid Metabolisers (%)
Africa	1.51%	6.38%
America	3.50%	4.94%
Europe	6.39%	4.27%
Middle East	1.63%	11.02%
Asia	0.56%	2.20%

The following table indicates the frequency of predicted CYP2D6 phenotypes identified in a cohort of 4,750 patients tested by *My DNA Life* and is thus likely to reflect the proportions in the broader Australian population.

Predicted CYP2D6 Phenotype	Predicted Codeine Response	%
Poor Metaboliser	No analgesic effect	5.66
Intermediate Metaboliser	Reduced analgesic effect	10.50
Extensive Metaboliser	Normal analgesic effect	80.89
Ultrarapid Metaboliser	Increased risk of toxicity	2.95

1.4 MyDNA Medication

My DNA Life currently offers CYP2D6 testing as part of a multi-gene test called MyDNA Medication (formerly DNAdose) that also identifies common polymorphisms in the genes encoding the enzymes CYP2C9, CYP2C19 and VKORC1. The results of the test help predict an

individual's metaboliser phenotype for each of these enzymes and therefore facilitate personalised prescribing to reduce some of the risks that inhere in pharmacotherapy.

The three cytochrome P450 enzymes included in the MyDNA Medication test are involved in the metabolism of up to 50% of commonly prescribed medications and the test results are therefore useful in guiding the prescription of many other medications in addition to codeine. For example:

- Tramadol is similarly bio-activated by CYP2D6 and therefore subject to the same therapeutic variability as codeine;
- Many antidepressants are metabolised by CYP2D6 and/or CYP2C19 and reduced metabolism can significantly increase blood levels and toxicity risk;
- Most proton-pump inhibitors are metabolised by CYP2C19 and ultra-rapid metabolisers may fail to achieve therapeutic blood levels;
- Most non-steroidal anti-inflammatory drugs (NSAIDs) are metabolised by CYP2C9 and reduced enzymatic activity has been associated with elevated blood levels and an increased risk of gastro-intestinal bleeding; and
- Clopidogrel is bio-activated by CYP2C19 and reduced metabolism is associated with decreased thrombotic protection.

2. Pharmacogenomics in the Pharmacy Setting

The reasons for the Delegate's interim decision listed on pages 12 to 17 include multiple references to the significant variability in codeine response as the result of genetic variation. In particular, point 4 on page 14 indicates that 'individuals rarely know their metaboliser status, and testing is not readily available'.

These limitations are largely the result of the traditional testing paradigm which is limited to doctors ordering the test as part of a clinical consultation. Whilst some medical practitioners use the test regularly, many clinicians are unfamiliar with the concept and feel uncomfortable explaining it to patients. These barriers have been well described in Australia (Corkingdale, Ward, and McKinnon 2007). In addition, the MyDNA Medication test is not covered by Medicare and therefore doctors need to take additional time to explain the test and its value to patients.

My DNA Life has recently concluded a pilot program in partnership with several Victorian pharmacies that involved the introduction of pharmacogenomic testing into the pharmacy setting to address many of these problems. Whilst patients are able to initiate the testing themselves, the results are initially sent to the pharmacist and a nominated doctor. This prevents unsupervised interpretation of the results by the patient which is a recognised problem of direct-to-consumer genetic testing.

Incorporating pharmacogenomics into pharmacy practice is also part of the Pharmacy Guild of Australia Roadmap and is supported by the Pharmaceutical Association of Australia. Providing pharmacogenomic testing in the pharmacy setting has been trialled elsewhere and determined to be successful (Swen *et al.* 2012; O'Connor *et al.* 2012).

2.1 The Testing Process

Testing is initiated in one of two ways:

a. The doctor identifies an indication for the test and refers their patient to a pharmacy for testing; or

b. The pharmacist suggests testing based on a patient's current or likely future medications.

Testing then proceeds as follows:

a. Patients are directed to a private consulting room where the pharmacist explains the testing in more depth and collects a DNA sample using a simple cheek swab. The patient's current medications are listed on the request form so that the results can be correlated with individual drugs;
b. The patient's sample is sent to a NATA-accredited laboratory for testing to identify a number of common polymorphisms in the four genes;
c. The raw genetic results are interpreted by a specialist team comprising a clinical geneticist, molecular geneticist, two clinical pharmacologists and a clinical pharmacist. Specific advice is provided regarding the likely effect of the patient's genetics on their current medications;
d. The report is sent to both the requesting pharmacist and the patient's nominated doctor;
e. The patient returns to the pharmacy to discuss the results with the pharmacist. If the report makes specific recommendations regarding the patient's current medications, they are encouraged to make an appointment to see their doctor; and
f. Patients are provided with an 'ID card' that summarises their results so that they can alert future prescribers to their metabolism profile. They are also provided with access to an online portal that allows them to check their genetic compatibility with a range of medications.

2.2 Results of the Trial

To date, over 600 tests have been conducted across 6 different pharmacies in Victoria. More than 300 doctors have been introduced to pharmacogenomic testing via the pharmacy program and have been provided with a genetic report for at least one of their patients that can help guide prescribing both now and in the future.

Testing of the first 370 patients identified:

- 11 patients with a genetic result predictive or CYP2D6 ultrarapid metabolism that places them at an increased risk of codeine toxicity;
- 65 patients with a genetic result predictive of negligible or significantly reduced CYP2D6 function that would likely render codeine therapy ineffective;

- 206 patients with a genetic result predictive of significantly reduced or increased CYP2C19 function; and
- 62 patients with a genetic result predictive of negligible or significantly reduced CYP2C9 function.

Of the 331 patients who had current medications listed on their request form:

- 52 (16%) were taking codeine;
- 19 (6%) were taking tramadol;
- 127 (38%) were taking a proton-pump inhibitor;
- 78 (24%) were taking an antidepressant significantly metabolised by CYP2C19;
- 99 (30%) were taking an antidepressant significantly metabolised by CYP2D6; and
- 55 (17%) were taking an NSAID.

3. References

Corkindale, D., Ward, H. and McKinnon, R. Low adoption of pharmacogenetic testing: an exploration and explanation of the reasons in Australia. Personalized Medicine. 2007; 4(2): 191-199.

Crews, K. R., *et.al.* Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for cytochrome P4502D6 (CYP2D6) genotype and codeine therapy: 2014 Update. Clinical pharmacology and therapeutics. 2014 Apr; 95(4):376-382.

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Llerena, A., *et al.* Interethnic variability of CYP2D6 alleles and of predicted and measured metabolic phenotypes across world populations. Expert opinion on drug metabolism and toxicology. 2014 Nov; 10(11): 1569-1583.

O'Connor, S. K., *et al*. Exploratory planning and implementation of a pilot pharmacogenetic program in community pharmacy. Pharmacogenomics. 2012 Jun; 13(8): 955-962.

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Appendix: Current CPIC guidelines for codeine therapy based on predicted CYP2D6 phenotype

Table 2 Codeine therapy recommendations based on cytochrome P450 2D6 (CYP2D6) phenotype

Phenotype	Implications for codeine metabolism	Recommendations for codeine therapy	Classification of recommendation for codeine therapy[a]	Considerations for alternative opioids
Ultrarapid metabolizer	Increased formation of morphine following codeine administration, leading to higher risk of toxicity	Avoid codeine use due to potential for toxicity.	Strong	Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity.[b,c]
Extensive metabolizer	Normal morphine formation	Use label-recommended age- or weight-specific dosing.	Strong	—
Intermediate metabolizer	Reduced morphine formation	Use label-recommended age- or weight-specific dosing. If no response, consider alternative analgesics such as morphine or a nonopioid.	Moderate	Monitor tramadol use for response.
Poor metabolizer	Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief	Avoid codeine use due to lack of efficacy.	Strong	Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity; these agents should be avoided.[b,c]

[a]Rating scheme is described in **Supplementary Data** online. [b]There is substantial evidence for decreased efficacy of tramadol in poor metabolizers and a single case report of toxicity in an ultrarapid metabolizer with renal impairment following tramadol use postsurgery. Use of other analgesics in CYP2D6 poor and ultrarapid metabolizers may therefore be preferable.[18,20,21] [c]Some other opioid analgesics, such as hydrocodone and oxycodone, are metabolized by CYP2D6. To avoid treatment complications, opioids that are not metabolized by CYP2D6, including morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone, along with nonopioid analgesics, may be considered as alternatives for use in CYP2D6 poor and ultrarapid metabolizers.

From: [redacted]
To: Medicines Scheduling
Subject: Note of concern
Date: [redacted]

Hello,

I was given this email address by my local chemist, who informed me that drugs like Mersyndol and any other containing codeine will soon require a prescription.

I just wanted to express my concern about this. If I get a severe [redacted], the last thing I want to do is go see a doctor. If it's after hours I'm completely [redacted]. I understand there are some dependency and misuse cases with codeine, but these products are already pharmacist-only medications. They can't be bought without undergoing a verbal interrogation (which I think is already way over the top).

Changing these laws will only hurt the average person seeking pain relief, and won't stop anyone from abusing them. They may just seek something even stronger if they're already going to the doctor.

Just my opinion. Thanks.

Australasian Medical
Review Officers Association

ABN 65142689727

Therapeutic Goods Administration
PO Box 100
Woden ACT 2606

15 October 2015

The Australasian Medical Review Officer's Association is supportive of the TGA's proposal to reschedule codeine from schedule 3 to 4.

Codeine has the potential to be abused and to cause impairment and it's availability over-the-counter increases the potential for use other than for appropriate therapeutic reasons, creating an increased workplace health and safety risk.

The schedule change will enable a doctor to more closely monitor usage and to take into consideration in prescribing decisions the person's occupation, associated risks and determine the fitness for duty ramifications of any medication that is prescribed.

Kind regards

[redacted]

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May 7, 2015

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[redacted]

RE: Codeine - Public Consultation on proposed amendments to the Poisons Standard

Thank you for the opportunity to provide comment upon the proposed amendments to the poisons standard. As you would be aware, the Faculty of Pain Medicine of the Australian and New Zealand College of Anaesthetists is the body responsible for the education, training and continuing professional development of specialist pain medicine physicians in Australia. The Faculty promotes appropriate prescribing for pain relief through its professional documents which are publicly available from http://www.fpm.anzca.edu.au/resources/professional-documents.

The Faculty strongly supports the deletion of codeine from schedule 3 and rescheduling to schedule 4 due to potential issues of morbidity, toxicity and dependence while being of limited analgesic benefit. This reclassification would be consistent with classification countries such as the United States, Sweden and Germany where all codeine containing preparation require prescription by a medical practitioner.[1]

1. **Adding low dose codeine to non-opioid analgesics provides little additional analgesic benefit**

Codeine (methylmorphine) is in practical terms an inactive prodrug of morphine, which requires metabolic conversion to morphine by Cytochrome P450 2D6 to be an active analgesic [2]. Codeine on its own is a poor analgesic; 12 patients need to be treated for one to achieve a 50% reduction in post-operative pain with a single 60 mg (NNT 12)[3]. While the combination of codeine with non-opioids such as paracetamol or ibuprofen

[1] Star investigation: Canada's invisible codeine problem http://www.thestar.com/news/canada/2015/01/17/star-investigation-canadas-invisible-codeine-problem.html [accessed April 24, 2015].

[2] Lotsch J (2005) Opioid metabolites. *J Pain Symptom Manage* **29**(5 Suppl): S10-24.

[3] Derry S, Moore RA, McQuay HJ. Single dose oral codeine, as a single agent, for acute postoperative pain in adults. Cochrane Database Syst Rev 2010;4:CD008099

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enhances the analgesic efficacy of these non-opioids, this requires combinations containing typically paracetamol 500 mg with codeine 30 mg per tablet such as in Panadeine forte™, already now a Schedule 4 drug.

2. **Ibuprofen 200mg/paracetamol 500mg OTC combinations provide increased analgesic benefit with less risk to the community.**

A number of studies have now identified that combinations of ibuprofen plus paracetamol provide superior analgesic efficacy to OTC codeine combination analgesics. One study and a meta-analysis reported that 1 or 2 tablets of a single-tablet combination of ibuprofen 200 mg/paracetamol 500 mg were statistically significantly more efficacious than 2 tablets of paracetamol 500 mg/codeine 15 mg. Two tablets offered significantly superior pain relief to ibuprofen 200 mg/codeine 12.8 mg (P = 0.0001), and 1 tablet was found noninferior to this combination [4]. This combination would continue to provide a good and safe OTC analgesic if codeine containing preparations would be rescheduled to Schedule 4 without the issues associated with opioid-containing analgesic combinations outlined below.

3. **Dependence on OTC codeine analgesics is a significant concern and can cause serious, sometimes life-threatening adverse effects due to the combination with paracetamol or NSAIDs**.

National and international media have focused attention on the significant and damaging impacts of codeine dependence on the community through featuring individual stories of the effects of codeine[5][6][7].

The dependence on and abuse of codeine containing combination preparations leads to significant organ toxicity due to the resulting consumption of excessive overdoses of the non-opioids paracetamol and ibuprofen in these combinations.

With regard to paracetamol, use of paracetamol containing codeine preparations exceeds the safe threshold of 4 g paracetamol in many abusers with high risk of liver toxicity of the excessive paracetamol doses consumed[8].

With regard to ibuprofen, Dr Malcolm Dobbin PhD MBBS DRANZCOG MPH FAFPHM, has collated an extensive list of studies and reported cases of impacts life threatening hypokalaemia from renal tubular acidosis as well as non-healing gastric ulcers unresponsive to treatment as a direct result of codeine abuse from 2008 through 2015 (appendix 1).

The current listing of codeine containing combinations with non-opioids as a schedule 3 drug is failing to protect the Australian community from the harmful side effects of these combination preparations with marginal analgesic benefit.

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[4] Daniels SE, Goulder MA, Aspley S, Reader S. A randomised, five-parallel-group, placebo-controlled trial comparing the efficacy and tolerability of analgesic combinations including a novel single-tablet combination of ibuprofen/paracetamol for postoperative dental pain. Pain 2011; 152;632–642; Ong CK, Seymour RA, Lirk P et al (2010) Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. *Anesth Analg* **110**(4): 1170-9.

[5] Yang, J. Star investigation: Canada's invisible codeine problem http://www.thestar.com/news/canada/2015/01/17/star-investigation-canadas-invisible-codeine-problem.html [accessed April 24, 2015].

[6] The Hoopla. Codeine addiction destroyed my family http://thehoopla.com.au/counter-addiction/ [accessed April 24, 2015].

[7] Marie Claire, National. Why addiction has never been so easy. 2015 pp42 – 46.

[8] Blieden M, Paramore LC, Shah D et al. A perspective on the epidemiology of acetaminophen exposure and toxicity in the United States. *Expert Rev Clin Pharmaco 2014:l* **7**(3): 341-8.

4. **Good evidence now demonstrates that under current arrangements (Schedule 3 Pharmacist Medicine) there is a substantial level of harm from the easy and widespread availability of these opioid medicines.**

Surveys of pharmacists and codeine dependent people seeking OTC codeine describe a number of themes about the difficulty of managing the safe supply of OTC codeine analgesics [9] [10] [11]. It is unreasonable to expect a pharmacist will be able to detect codeine dependence based solely on a customer's appearance.

Thank you for the opportunity to provide feedback. Should you require any further information, please contact [redacted], General Manager, Policy, via email [redacted] or telephone [redacted].

Kind Regards

[redacted]

[9] Nielsen S, Cameron J, Pahoki S. Over the counter codeine dependence final report 2010. Victoria: Turning Point, 2010. http://atdc.org.au/wp-content/uploads/2011/02/OTC_CODEINE_REPORT.pdf

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[11] Cooper R. Surveillance and uncertainty: community pharmacy responses to over the counter medicine abuse. Health Soc Care Community 2013;21:254-62.