Final decisions and reasons for decisions by delegates of the Secretary to the Department of Health and Ageing

June 2013

Notice under subsections 42ZCZS and 42ZCZX of the Therapeutic Goods Regulations 1990 (the Regulations)

A delegate of the Secretary to the Department of Health and Ageing hereby gives notice of the delegates' final decisions for amending the Poisons Standard (commonly referred to as the *Standard for the Uniform Scheduling of Medicines and Poisons* – SUSMP) under subsections 42ZCZS and 42ZCZX of the Therapeutic Goods Regulations 1990 (the Regulations). This notice also provides the reasons for each decision and the date of effect (implementation date) of the decision.

The delegates' final decisions and reasons relate to:

- scheduling proposals initially referred to the March 2013 meeting of the Advisory Committee on Chemicals Scheduling (ACCS#7);
- scheduling proposals initially referred to the March 2013 meeting of the Advisory Committee on Medicines Scheduling (ACMS# 8);
- scheduling proposals initially referred to the March 2013 joint meeting of the ACCS and the ACMS (joint ACCS-ACMS#5);
- scheduling proposals considered as delegate-only matters, i.e. not referred to an expert advisory committee.

Scheduling proposals referred to the expert advisory committees

Pre-meeting public notice

The first 'pre-meeting' public notice inviting submissions on the scheduling proposals referred to the expert advisory committees was published on 29 November 2012 at http://www.tga.gov.au/newsroom/consult-scheduling-acmcs-1303.htm and the second public notice was published on 7 February 2013 at http://www.tga.gov.au/newsroom/consult-scheduling-accs-1303.htm**.**

Redacted versions of the public submissions received in response to this invitation were published on 23 May 2013 at http://www.tga.gov.au/industry/scheduling-submissions-1303.htm.

Interim decisions

The delegates' interim decisions on recommendations by the ACCS#7, ACMS#8 and joint ACCS-ACMS#5 were published on 23 May 2013 at http://www.tga.gov.au/industry/scheduling-decisions-1305-interim.htm. This public notice also invited further comment from the applicant and from those parties who made a valid submission in response to the original invitation for submissions.

Further submissions from parties other than those who made a valid submission in response to the original invitation or the applicant, or those received after the closing date, may not be considered by the delegate.

Redacted versions of public submissions received in response to the interim decisions were published on 27 June 2013 at http://www.tga.gov.au/industry/scheduling-submissions.htm.

Final decisions

In accordance with subsection 42ZCZR of the Regulations, if a delegate makes an interim decision on an application, the delegate may make a final decision either confirming varying or setting aside the interim decision, but only after considering any valid submissions received in response to the interim decisions.

Matters not referred to an advisory committee

A delegate may decide not to refer a scheduling proposal to an expert advisory committee for advice and instead may make a delegate-only decision. When deciding not to refer a matter to a committee, the delegate considers the scheduling guidelines as set out in the *Scheduling Policy Framework* (SPF), available at http:www.tga.gov.au/industry/scheduling-spf.htm.

Publishing of the amendments to the Poisons Standard

The amendments to the Schedules, Appendices or other parts of the Poisons Standard are published electronically on ComLaw and in a hardcopy Amendment to the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) prior to the date of effect (implementation date) of the final decisions. Further information, including links to the Poisons Standard on ComLaw, is available at http:www.tga.gov.au/industry/scheduling-poisons-standard.htm.

Table of contents

Glossary

Abbreviation	Name
AAN	Australian Approved Name
AC	Active constituent
ACCC	Australian Competition and Consumer Commission
ACCM	Advisory Committee on Complementary Medicines (formerly Complementary Medicine Evaluation Committee [CMEC])
ACNM	Advisory Committee on Non-prescription Medicines (formerly Medicines Evaluation Committee [MEC])
ACPM	Advisory Committee on Prescription Medicines (formerly Australian Drug Evaluation Committee [ADEC])
ACSOM	Advisory Committee on the Safety of Medicines (formerly Adverse Drug Reactions Advisory Committee [ADRAC])
ADEC	Australian Drug Evaluation Committee (now Advisory Committee on Prescription Medicines [ACPM])
ADI	Acceptable daily intake
ADRAC	Adverse Drug Reactions Advisory Committee (now Advisory Committee on the Safety of Medicines [ACSOM])
AHMAC	Australian Health Ministers' Advisory Council
APVMA	Australian Pesticides and Veterinary Medicines Authority
AQIS	Australian Quarantine and Inspection Service
ARfD	Acute reference dose
ASCC	Australian Safety and Compensation Council
ASMI	Australian Self-Medication Industry
ARTG	Australian Register of Therapeutic Goods

Abbreviation	Name
CAS	Chemical Abstract Service
CHC	Complementary Healthcare Council of Australia
CMEC	Complementary Medicine Evaluation Committee (now Advisory Committee on Complementary Medicines [ACCM])
CMI	Consumer Medicine Information
COAG	Councils of Australian Governments
CRC	Child-resistant closure
CTFAA	Cosmetic, Toiletry & Fragrance Association of Australia
CWP	Codeine Working Party
DAP	Drafting Advisory Panel
ECRP	Existing Chemicals Review Program
EPA	Environmental Protection Authority
ERMA	Environmental Risk Management Authority (New Zealand)
FAISD	First Aid Instructions and Safety Directions
FDA	Food and Drug Administration (United States)
FOI	Freedom of Information Act 1982
FSANZ	Food Standards Australia New Zealand
GHS	Globally Harmonised System for Classification and Labelling of Chemicals
GIT	Gastro-intestinal tract
GP	General practitioner
HCN	Health Communication Network

Abbreviation	Name
INN	International Non-proprietary Name
ISO	International Standards Organization
LC50	The concentration of a substance that produces death in 50% of a population of experimental organisms. Usually expressed as mg per litre (mg/L) as a concentration in air.
LD50	The concentration of a substance that produces death in 50% of a population of experimental organisms. Usually expressed as milligrams per kilogram (mg/kg) of body weight.
LOAEL	Lowest observed adverse effect level
LOEL	Lowest observed effect level
MCC	Medicines Classification Committee (New Zealand)
MEC	Medicines Evaluation Committee (now Advisory Committee on Non-prescription Medicines [ACNM])
MOH	Ministry of Health (New Zealand)
NCCTG	National Coordinating Committee on Therapeutic Goods
NDPSC	National Drugs and Poisons Schedule Committee
NHMRC	National Health and Medical Research Council
NICNAS	National Industrial Chemicals Notification & Assessment Scheme
NOAEL	No observed adverse effect level
NOEL	No observable effect level
NOHSC	National Occupational Health & Safety Commission
OCM	Office of Complementary Medicines
OCSEH	Office of Chemical Safety and Environmental Health (now Office of Chemical Safety [OCS])

Abbreviation	Name
OCS	Office of Chemical Safety (formerly Office of Chemical Safety and Environmental Health [OCSEH])
ODA	Office of Devices Authorisation
OMA	Office of Medicines Authorisation (formerly Office of Prescription and Non-prescription Medicines)
OOS	Out of session
OTC	Over-the-counter
PACIA	Plastics and Chemicals Industries Association
PAR	Prescription animal remedy
PBAC	Pharmaceutical Benefits Advisory Committee
PEC	Priority existing chemical
PGA	Pharmaceutical Guild of Australia
PHARM	Pharmaceutical Health and Rational Use of Medicines
PI	Product Information
PIC	Poisons Information Centre
PSA	Pharmaceutical Society of Australia
QCPP	Quality Care Pharmacy Program
QUM	Quality Use of Medicines
RFI	Restricted flow insert
SCCNFP	Scientific Committee on Cosmetic and Non-Food Products
SCCP	Scientific Committee on Consumer Products
STANZHA	States and Territories and New Zealand Health Authorities

Abbreviation	Name
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
SVT	First aid for the solvent prevails
TCM	Traditional Chinese medicine
TGA	Therapeutic Goods Administration
TGC	Therapeutic Goods Committee
TGO	Therapeutic Goods Order
TTHWP	Trans-Tasman Harmonisation Working Party
TTMRA	Trans-Tasman Mutual Recognition Agreement
WHO	World Health Organization
WP	Working party
WS	Warning statement

Part A - Final decisions on matters referred to an expert advisory committee

1. Scheduling proposals referred to the March 2013 meeting of the Advisory Committee on Chemicals Scheduling (ACCS#7)

1.1 Abamectin

Scheduling proposal

The Chemicals Scheduling Delegate considered a proposal to amend abamectin Schedule 6(a) entry to raise the cut-off from 2 to 4 per cent or less of abamectin in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).

The delegate referred the proposal to the Advisory Committee on Chemicals Scheduling (ACCS) for advice.

Scheduling status

Abamectin is currently listed in Schedules 5, 6 and 7 and Appendix J.

Scheduling history

In November 1984, the Poisons Schedule (Standing) Committee (PSC) considered scheduling of a 1 per cent avermectin B1 (a synonym for abamectin) injection to be used as an antiparasitic agent in animals. Based on toxicity, PSC decided to include this substance in Schedule 7. However, the PSC also noted the intent to only market a sealed container product for use with automated injection equipment and agreed to a Schedule 6 cut-off for such preparations when included in 10 mL or less injections.

In May 1992, the Drugs and Poisons Schedule Standing Committee agreed to a request to change the name of avermectin B1 in the schedule entries to abamectin, noting that this was the name approved by the Standards Association of Australia (now called Standards Australia).

In August 1994, the National Drugs and Poisons Schedule Committee (NDPSC) decided to include emulsifiable concentrate formulations containing abamectin at 18 g/L or less in Schedule 6.

In August 1995, NDPSC agreed to include ≤ 1 per cent abamectin for animal internal use in Schedule 5.

In June 2008, the NDPSC decided also to include slow-release plastic matrix ear tags for livestock use containing 1 g or less of abamectin in Schedule 6.

In October 2009, the NDPSC considered whether preparations for pesticidal use containing 0.0015 per cent or less of abamectin were consistent with the Schedule 5 criteria. It was agreed that although low concentration of abamectin were likely to be less hazardous, because insufficient data had been provided to allay the concern regarding the high acute oral, dermal and inhalation toxicity of abamectin, it was decided that the existing scheduling was appropriate, i.e. no changes.

Public pre-meeting submissions

No public submissions were received.

ACCS advice to the delegate

The ACCS recommended that the Schedule 6 cut-off for abamectin for pesticidal use be increased from 2 per cent to 4 per cent or less of abamectin.

The ACCS recommended an implementation date of 1 September 2013.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included; (a) the risks and benefits of the use of a substance, (b) the purpose for which a substance is to be used and the extent of use of a substance, (d) the dosage, formulation, labelling, packaging and presentation of a substance and (f) any other matters.

The reasons for the recommendation comprised the following:

- The product was efficient against certain mites and insect pests of food crops.
- The risk of health effects associated with potential exposures have been adequately addressed.
- The MOE values were sufficient and a 1000-fold safety factor was considered to be protective of all toxicological findings.

Delegate's interim decision

The delegate decided to accept the ACCS advice and to increase the Schedule cut-off to 4 per cent.

The proposed implementation date for this decision is 1 September 2013.

The relevant matters considered by the delegate under section 52E (1) of the *Therapeutic Goods Act 1989* includes (c) the toxicity.

The decision to increase the Schedule 6 cut-off from 2 per cent to 4 per cent or less for abamectin for pesticidal use incorporated the following reasons:

- The toxicity of abamectin is well characterised and increasing the Schedule 6 cut-off from 2 per cent to 4 per cent retains an adequate margin of exposure for workers using this product.

Submissions on interim decision

No submissions were received.

Delegate's consideration

The delegate considered the following in regards to this proposal:

- the evaluation report (not publically available);
- scheduling proposal;
- ACCS advice;
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[1]; and
- other relevant information.

[1] Scheduling Policy Framework for Medicines and Chemicals <http://www.tga.gov.au/industry/scheduling-spf.htm>

Delegate's final decision

The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

Schedule entry

Schedule 6 – Amendment

ABAMECTIN – Amend entry to read:

ABAMECTIN:

(a) in preparations for pesticidal use containing ~~2~~ 4 per cent or less of abamectin **except** when included in Schedule 5; or

(b) in slow-release plastic matrix ear tags for livestock use containing 1 g or less of abamectin.

1.2 Carbonyl sulfide

Scheduling proposal

The Chemicals Scheduling Delegate considered a proposal to create new Schedule 7 and Appendix J entries for carbonyl sulfide in the *Standard for the Uniform Scheduling of Medicines and Poisons*.

The delegate referred the proposal to the Advisory Committee on Chemicals Scheduling (ACCS) for advice.

Scheduling history

Carbonyl sulfide has not been considered previously.

Current scheduling status

Carbonyl sulfide is not listed in the SUSMP.

Public pre-meeting submissions

No public submissions were received.

ACCS advice to the delegate

The ACCS recommended that carbonyl sulfide when packed and labelled for use as a fumigant be included in Schedule 7.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included; (a) the risks and benefits of the use of a substance, (b) the purpose for which a substance is to be used and the extent of use of a substance, (c) toxicity and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The following reasons were noted:

- Carbonyl sulfide was efficient against stored grain pests and imported biological products. It would be an efficient substitute for other toxic fumigants.
- There was a risk of acute toxicity for applicators and bystanders.

- Carbonyl sulfide has a steep acute dose response curve and neurotoxicity.
- Toxicological database was limited.
- The toxicity profile of COS satisfies the criteria for Schedule 7.
- As a fumigant, it will require specialist training and equipment for use.

Delegate's interim decision

The delegate accepts the recommendation of the ACCS that carbonyl sulfide be listed in Schedule 7 and Appendix J.

The proposed implementation date for this decision is 1 September 2013.

The relevant matters considered by the delegate under section 52E (1) of the *Therapeutic Goods Act 1989* includes (a) the risks and benefits (b) the purpose, (c) the toxicity and (d) the dosage, formulation, labelling, packaging and presentation.

The decision to include carbonyl sulfide in Schedule 7 and Appendix J incorporated the following reasons:

- Carbonyl sulfide has the potential to cause neurotoxicity and must be carefully handled. However, the availability of an alternate fumigant to possibly replace other more toxic fumigants is a potential benefit.
- The acute toxicity of Carbonyl sulfide appears to fit with Schedule 6 criteria, but the steepness of the dose-response curve, the potential for neurotoxicity with chronic exposure, and the gaps in the available toxicity data suggest that Schedule 7 would be more appropriate.
- Workers using Carbonyl sulfide as a fumigant will need appropriate training and specialist equipment to mitigate exposure.

Submissions on interim decision

No submissions were received.

Delegate's consideration

The delegate considered the following in regards to this proposal:

- the evaluation report (not publically available);
- scheduling proposal;
- ACCS advice;
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[2]; and
- other relevant information.

[2] Scheduling Policy Framework for Medicines and Chemicals <http://www.tga.gov.au/industry/scheduling-spf.htm>

Delegate final decision

The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

Schedule entry

Schedule 7 – New entry

CARBONYL SULFIDE when packed and labelled for use as a fumigant.

Appendix J Part 2 – New entry

Poison	Conditions
Carbonyl sulfide	1

1.3 Chlorfenapyr

Scheduling proposal

The Chemicals Scheduling Delegate considered a proposal to create a new Schedule 5 entry for preparations containing 0.5 per cent or less chlorfenapyr, with consequent amendments to the current Schedule 7 and Schedule 6 entries in the *Standard for the Uniform Scheduling of Medicines and Poisons*.

The delegate referred the proposal to the Advisory Committee on Chemicals Scheduling (ACCS) for advice.

Scheduling status

Preparations containing 36 per cent or less chlorfenapyr are listed in Schedules 6 and all other preparations are listed in Schedule 7.

Scheduling history

In February 1996, the NDPSC considered the scheduling of chlorfenapyr. The NDPSC noted that in the dog an approximate oral LD_{50} of 9 mg/kg was determined when a single dose of 10 mg/kg resulted in the rapid death of 2 females. In chronic rat and dog dietary studies high doses were also reported to cause mild non-regenerative anaemia, which was unrelated to blood loss. A NOEL of 2.6 mg/kg/day in a rat dietary study was based on reduced weight gain and neurological lesions in male rats receiving higher doses. A NOEL of 2.1 mg/kg/day was determined in a 12 month dog study based on elevated creatinine levels in dogs receiving higher doses. In a rat developmental study no significant abnormalities were seen at the highest dose of 225 mg/kg/day. Based on the toxicology profile of chlorfenapyr, the NDPSC decided to include it in Schedules 6 and 7.

ACCS advice to the delegate

The ACCS recommended that chlorfenapyr in preparations containing 0.5 per cent or less of chlorfenapyr be included in Schedule 5.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included; (a) the risks and benefits of the use of a substance, (b) the purpose for which a

substance is to be used and the extent of use of a substance, (c) toxicity and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The following reasons were noted:

- Chlorfenapyr is efficient against domestic and commercial insect and arachnid pests.
- Risk arises from the mechanism of toxicity of the product and its LD_{50}.
- Dosage and formulation fits the criteria for Schedule 5, i.e. available in a ready use pack and the risk is reduced by the packaging.

Delegate's interim decision

The delegate accepts the advice of the ACCS and agrees that products containing 0.5 per cent or less meet criteria for listing in Schedule 5. Accordingly, the delegate proposes to create a new Schedule 5 entry for chlorfenapyr.

The proposed implementation date for this decision is 1 September 2013.

The relevant matters considered by the delegate under section 52E (1) of the *Therapeutic Goods Act 1989* includes (c) the toxicity and (d) the dosage, formulation, labelling, packaging and presentation.

The decision to include 0.5 per cent or less chlorfenapyr in Schedule 5 incorporated the following reasons:

- The toxicity of chlorfenapyr is well characterised and creating a new Schedule 5 entry for a product containing 0.5 per cent retains an adequate margin of exposure for workers using this product.
- The product under consideration is to be formulated in a ready-use pack, which is expected to minimise exposure potential for workers using the product.

Submissions on interim decision

No submissions were received.

Delegate's consideration

The delegate considered the following in regards to this proposal:

- the evaluation report (not publically available);
- scheduling proposal;
- ACCS advice;
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[3]; and
- other relevant information.

[3] Scheduling Policy Framework for Medicines and Chemicals <http://www.tga.gov.au/industry/scheduling-spf.htm>

Delegate's final decision

The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

Schedule entry

Schedule 5 - New entry

CHLORFENAPYR in preparations containing 0.5 per cent or less of chlorfenapyr.

Schedule 6 - Amendment

CHLORFENAPYR – Amend entry to read:

CHLORFENAPYR in preparations containing 36 per cent or less of chlorfenapyr **except** when included in Schedule 5.

Schedule 7 - Amendment

CHLORFENAPYR – Amend entry to read:

CHLORFENAPYR **except** when included in Schedules 5 or 6.

1.4 Eubacterium sp

Scheduling proposal

The Chemicals Scheduling Delegate considered a proposal to create a new Schedule 5 entry for *Eubacterium* sp in the *Standard for the Uniform Scheduling of Medicines and Poisons*.

The delegate referred the proposal to the Advisory Committee on Chemicals Scheduling (ACCS) for advice.

Scheduling status

Eubacterium sp. is not specifically scheduled.

Scheduling history

In February 2009, the NDPSC considered scheduling of *Eubacterium* sp. strain DSM 11798. The NDPSC noted that strain DSM 11798 had low acute dermal toxicity in rats, was not a skin or eye irritant in rabbits and was not a skin sensitiser in guinea pigs. The applicant also submitted a 90-day sub-chronic oral study in rats, but no acute oral study nor a scientific argument as to why one was not provided. The NDPSC noted that strain DSM 11798 showed no evidence of toxicity or adverse effects up to 4.52×10^5 CFU/kg bw/day, equivalent to 200 mg/kg bw/day, via repeated oral administration. The NOEL was therefore > 4.52×10^5 CFU/g or 200 mg/kg bw/day. The NDPSC noted that there were insufficient data provided on various toxicity studies and decided not to make a scheduling decision.

Public pre-meeting submissions

No public submissions were received.

ACCS advice to the delegate

The ACCS decided that it is unable to make a scheduling recommendation on *Eubacterium* sp. or on strain DSM11798 on the basis of the insufficiency of the data provided.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included; (a) the risks and benefits of the use of a substance, (b) the purpose for which a substance is to be used and the extent of use of a substance, (c) the toxicity and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the recommendation comprised the following:

- reduction of adverse effects of feed mycotoxins in intensive animal production.
- additive to feed of pigs and poultry to minimise the effects of feed mycotoxins. Potentially widespread use in animal industries.
- insufficient data on the specific characteristics of the organism to species level and quality assurance for the strain purity.
- in addition, requiring informed comment on substrate specificity.
- insufficient data on potential human pathogenicity and/or infectivity of the organism by all potential exposure routes, including intramuscular and intraperitoneal and intredermal.
- submitted data indicated low toxicity except for acute inhalation.
- presentation as a coarse particle feed premix.

Delegate's interim decision

The delegate has decided to make a new entry for *Eubactrium* sp. strain DSM11798 in Appendix B.

The proposed implementation date for this decision is 1 September 2013.

The relevant matters considered by the delegate under section 52E (1) of the *Therapeutic Goods Act 1989* includes (a) the risks and benefits and (c) the toxicity.

The decision to include *Eubactrium* sp. strain DSM11798 in Appendix B incorporated the following reasons:

- this bacterial product has low toxicity and mild irritancy potential. The mild irritancy potential could be linked with physical abrasivity of formulation ingredients rather than the bacteria itself.
- the applicant had adequately determined the pathogenicity of the naturally-occurring bacterial strain, low pathogenicity could be inferred from the arguments presented (mainly around it being an obligate anaerobe). The lack of specific pathogenicity tests should not be a reason to further defer a scheduling decision.
- overall toxicity profile was consistent with several other bacterial substances currently listed in Appendix B, and accordingly the delegate decided to accept the recommendation of the evaluation report to make a new entry in Appendix B for *Eubactrium* sp. strain DSM11798.

Submissions on interim decision

One submission, from a party who did not make a valid submission in response to the original invitation, was received.

The submission indicated that European Food Safety Authority (EFSA) report on the *Eubacterium* concluded that although the additive is formulated to minimise exposure by inhalation some exposure of the respiratory tract remains possible and potential for respiratory sensitization cannot be excluded. As such there is the possibility that it may add weight to the argument for Schedule 5 listing for *Eubacterium* sp rather than an Appendix B listing.

The redacted submission is available at http://www.tga.gov.au/industry/scheduling-submissions.htm.

Delegate's consideration

The delegate considered the following in regards to this proposal:

- the evaluation report (not publically available);
- scheduling proposal;
- ACCS advice;
- Public submissions;
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[4]; and
- other relevant information.

Delegate final decision

The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

The delegate has considered the public submission (including the EFSA report) on delegate's interim decision in support of consideration of a Schedule 5 entry. However, this report had already been considered by the ACCS and the delegate when making the interim decision.

Schedule entry

Appendix B, PART 3 New entry

Substance	Date of entry	Reason for listing	Area of use
Eubacterium sp. strain DSM11798	Sep 2013	a	2.4

1.5 Pyroxasulfone

Scheduling proposal

The Chemicals Scheduling Delegate considered a proposal to delete the current pyroxasulfone Schedule 7 entry and amend the current Schedule 6 entry to a simple entry with no exemptions in the *Standard for the Uniform Scheduling of Medicines and Poisons*.

[4] Scheduling Policy Framework for Medicines and Chemicals <http://www.tga.gov.au/industry/scheduling-spf.htm>

The delegate referred the proposal to the Advisory Committee on Chemicals Scheduling (ACCS) for advice.

Scheduling status

Pyroxasulfone is listed in Schedules 6 and 7.

Scheduling history

In September 2011, the delegate decided to create new Schedules 6 and 7 entries for pyroxasulfone. This decision included a cut-off to Schedule 6 from Schedule 7 for water dispersible granule preparations when used as a pre-emergence herbicide.

The delegate made this decision following the recommendation from the ACCS. The ACCS noted that while there were minimal acute toxicity concerns, there were serious repeat dose concerns, noting effects on the cardiac muscle even in short term studies. In addition to the cardiac concerns, there were nerve tissue effects at quite low exposure levels, and developmental neurotoxicity in longer term study. The ACCS also noted that a high margin of exposure (MOE) had been determined by the evaluator. However, the ACCS felt that the severity of the endpoints was such that the ACCS could not ignore the possibility of exposure. The Committee generally agreed that Schedule 7 was appropriate for the pyroxasulfone parent entry.

The ACCS noted that the evaluator had asked for a cut-off to Schedule 6 for products containing 85 per cent or less pyroxasulfone for pre-emergence herbicidal use. The ACCS agreed that the percentage component was unnecessary, particularly as the toxicity difference between the high concentration cut-off and the 100 per cent substance was likely to be minimal.

The ACCS noted that the likely exposure to pyroxasulfone given the use pattern was dermal and via inhalation, and that repeat dermal exposure was the main concern. The ACCS noted that this concern was significant enough to not allow any cut-offs from a Schedule 7 parent entry. The ACCS contended, however, that this concern was sufficiently mitigated for water dispersible granule formulations, due to their lower absorption potential. The ACCS suggested that this presentation could be the basis for a cut-off to Schedule 6. The ACCS agreed, noting the high MOEs determined by the evaluator for the water dispersible formulations, its minimised exposure potential and the additional risk mitigation measures intended to be implemented by the regulator through labelling.

ACCS advice to the delegate

The ACCS recommended that pyroxasulfone be rescheduled from Schedule 7 to Schedule 6 with no cut-offs.

The ACCS recommended an implementation date of 1 September 2013.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included; (a) the risks and benefits of the use of a substance, (c) the toxicity of a substance, (d) the dosage, formulation, labelling, packaging and presentation of a substance and (f) any other matters that the Secretary considers necessary to protect public health.

The following reasons were noted:

- New data allowing more informed judgement showing that findings, whilst still treatment-related, were not toxicologically significant.
- Pyroxasulfone is no longer considered to be a developmental neurotoxicant.

- It would be unlikely that there would be any variation in toxicity between 100 per cent and 85 per cent.
- Lack of data to determine a cut-off.

Delegate's interim decision

The delegate has decided to accept the advice of the ACCS and the scheduling recommendation of the evaluation report, and consolidate the scheduling of pyroxasulfone in Schedule 6, with no cut-off.

The proposed implementation date for this decision is 1 September 2013.

The relevant matters considered by the delegate under section 52E (1) of the *Therapeutic Goods Act 1989* includes (c) the toxicity and (d) the dosage, formulation, labelling, packaging and presentation.

The decision to include pyroxasulfone in Schedule 6, with no cut-off incorporated the following reasons:

- The primary reason for including pyoxasulfone in Schedule 7 when originally scheduled was concern over its developmental neurotoxicity potential. This concern has been ameliorated by the presentation of new data and argument relating to the signal toxic event in rat studies. While the human relevance of the renal papillary tumours seen in male rats is still not completely resolved, the delegate agrees with the ACCS that this finding does not warrant retaining pyroxasulfone in Schedule 7.
- The high concentration of pyoxasulfone in the product under consideration does not allow for differentiation of its toxicity from the technical grade active substance. Hence no cut-off to a lower schedule is proposed.

Delegate's consideration

The delegate considered the following in regards to this proposal:

- the evaluation report (not publically available);
- scheduling proposal;
- ACCS advice;
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[5]; and
- other relevant information.

Delegate's final decision

The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

[5] Scheduling Policy Framework for Medicines and Chemicals <http://www.tga.gov.au/industry/scheduling-spf.htm>

Schedule entry

Schedule 6 – Amendment

PYROXASULFONE – Amend entry to read:

PYROXASULFONE ~~in water dispersible granule preparations when for pre-emergence herbicide use~~.

Schedule 7 – Amendment

PYROXASULFONE – Delete entry

~~PYROXASULFONE **except** when included in Schedule 6.~~

1.6 Sulfoxaflor

Scheduling proposal

The Chemicals Scheduling Delegate considered a proposal to create a new Schedules 6 and/or 5 entries for sulfoxaflor in the *Standard for the Uniform Scheduling of Medicines and Poisons*.

The delegate referred the proposal to the Advisory Committee on Chemicals Scheduling (ACCS) for advice.

Scheduling status

Sulfoxaflor is not specifically scheduled.

Other neonicotinoid insecticides such as, clothianidin, imidacloprid, thiamethoxam are listed in Schedules 5 and 6, and nitenpyram, thiacloprid, and acetamiprid are listed in Schedule 6.

Scheduling history

Sulfoxaflor was not considered for scheduling previously.

Public pre-meeting submissions

No public submissions were received.

ACCS advice to the delegate

The ACCS recommended that sulfoxaflor be included in Schedule 6 with a cut-off to Schedule 5 for preparations containing less than 25 per cent of sulfoxaflor.

The ACCS recommended an implementation date of 1 September 2013.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included; (a) the risks and benefits of the use of a substance, (b) the purpose, (c) the toxicity of a substance and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The following reasons were noted:

- Efficient against damaging insect pests and many agricultural and horticultural crops.
- Toxic effects to applicator therefore require PPEs and label warning statements.
- Not for domestic use.

- Moderate toxicity of the active ingredient and lower toxicity of the preparation containing 24 per cent sulfoxaflor.

Delegate's interim decision

The delegate accepts the advice of the ACCS and agrees that sulfoxaflor meets criteria for listing in Schedule 6. The delegate also proposes to create a new Schedule 5 entry for products containing 25 per cent or less sulfoxaflor.

The proposed implementation date for this decision is 1 September 2013.

The relevant matters considered by the delegate under section 52E (1) of the *Therapeutic Goods Act 1989* includes (c) the toxicity and (d) the dosage, formulation, labelling, packaging and presentation.

The decision to include sulfoxaflor in Schedules 5 and 6 incorporated the following reasons:

- The acute and chronic toxicity profiles of sulfoxaflor are consistent with the criteria for Schedule 6. The delegate accepts ACCS advice that the human relevance of the observed hepatocellular adenomas and Leydig cell tumours in rats is adequately addressed by the MOA studies.
- The proposed product containing 24 per cent sulfoxaflor demonstrates an adequate margin of exposure (MOE) estimates for its use by workers when used with appropriate personal protective equipment (PPE). This, along with its reduced acute toxicity profile justifies inclusion of the product in a lower schedule (Schedule 5).
- The basic recommendation that sulfoxaflor be included in Schedule 6 with a cut-off to Schedule 5, has been adopted, but a minor change to the Schedule 5 wording is proposed for consistency with other SUSMP entries relating to cut-offs.

Submissions on interim decision

No submissions were received.

Delegate's consideration

The delegate considered the following in regards to this proposal:

- the evaluation report (not publically available);
- scheduling proposal;
- ACCS advice;
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[6]; and
- other relevant information.

Delegate final decision

The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

[6] Scheduling Policy Framework for Medicines and Chemicals <http://www.tga.gov.au/industry/scheduling-spf.htm>

Schedule entry

Schedule 5 – New entry

SULFOXAFLOR in preparations containing 25 per cent or less of sulfoxaflor.

Schedule 6 – New entry

SULFOXAFLOR **except** when included in Schedule 5.

2. Scheduling proposals referred to the March 2013 meeting of the Advisory Committee on Medicines Scheduling (ACMS#8)

2.1 Benzodiazepines

Scheduling proposal

The medicines scheduling delegate considered a proposal to reschedule benzodiazepines from Schedule 4 to Schedule 8 in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).

The delegate referred the proposal to the Advisory Committee on Medicines Scheduling (ACMS) for advice.

Scheduling history

In May 1982, the general class of benzodiazepines was included into Schedule 4. In May 1986, individual benzodiazepine substances were listed in Schedule 4 (bromazepam, diazepam).

A review of scheduling for the benzodiazepine class of drugs in August 1998 found that the benzodiazepines entries in Schedule 4 remained appropriate, with the expectation of the substance flunitrazepam, which was included in Schedule 8 in November 1997 based on public health concerns associated with abuse of this substance.

The rescheduling of Alprazolam as a Schedule 8 substance was considered by the National Drugs and Poisons Scheduling Committee in June 2010, after the up-scheduling of Flunitrazepam. The committee stated that there was insufficient evidence to support a Schedule 8 restriction for alprazolam and agreed that until such information is provided to support a rescheduling application, the Schedule 4 entry remained appropriate.

Current scheduling status

Group listing of benzodiazepine derivatives is included in Schedule 4. Other specific benzodiazepines are also included in Schedule 4 (other than flunitrazepam) and in Appendix K.

Public pre-meeting submissions

Seventy public pre-meeting submissions were received.

Fifty-two of those submissions were against the rescheduling of benzodiazepines on the grounds of negative impact to business. The main impacts related to increased administrative burden and the need to increase security for those who administer or dispense benzodiazepines, such as aged care facilities and pharmacies.

Sixteen submissions were in support of rescheduling benzodiazepines in Schedule 8 citing public health concerns associated with the abuse and trafficking of these substances.

Two submissions did not provide comment either for or against. One noted the misuse of alprazolam; the other outlined business impacts should the proposal go ahead.

At least 12 submissions—both for and against—suggested that alprazolam be included under Schedule 8 due to concerns regarding abuse of this substance.

The redacted public submissions are available at http://www.tga.gov.au/industry/scheduling-submissions.htm.

ACMS advice to the delegate

The ACMS recommended that alprazolam be rescheduled from Schedule 4 to Schedule 8 and that that the scheduling of the remaining benzodiazepines remains appropriate. The ACMS also recommends that benzodiazepines be included in Appendix D, paragraph 5.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included; (a) the risks and benefits of the use of a substance, (b) the purposes for which a substance is to be used and the extent of use of a substance, (c) the toxicity of a substance, (d) the dosage, formulation, labelling, packaging and presentation of a substance and (e) the potential for abuse of a substance.

The reasons for the recommendation comprised the following:

- alprazolam: a public health problem of widespread use with possible increased toxicity. It does not appear to have any additional therapeutic benefits compared with any other substance in the class.
- alprazolam: listing in Schedule 8 does not restrict short-term use for the approved indication. There has also been a rapid increase in use compared with other benzodiazepines.
- alprazolam: increased morbidity and mortality in overdose. Misuse, particularly in association with opioids.
- alprazolam: pack size and potency of dosage forms. Pack size inappropriate for approved indication.
- alprazolam: evidence of widespread misuse.

Delegates interim decision

The delegate made the following interim decision regarding the scheduling proposal:

- That alprazolam be rescheduled from Schedule 4 to Schedule 8;
- That the scheduling of the remaining benzodiazepines remains appropriate; and
- That benzodiazepines be included in Appendix D, paragraph 5.

The delegate decided that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* include (a) the risks and benefits of the use of a substance, (b) the purposes for which a substance is to be used and the extent of use of a substance, (c) the toxicity of a substance, (d) the dosage, formulation, labelling, packaging and presentation of a substance and (e) the potential for abuse of a substance.

The reasons for the interim decision comprised the following:

- Alprazolam has increased morbidity and mortality in overdose with possible increased toxicity. It does not appear to have any additional therapeutic benefits compared with any other substance in the class.
- There has also been a rapid increase in use of Alprazolam compared with other benzodiazepines and evidence of widespread misuse.
- Alprazolam - Concerns of possible increased toxicity.
- Alprazolam - concern that current pack size is inappropriate for indications.
- There is evidence of abuse of the substance and misuse with opiods.
- Listing in Schedule 8 of Alprazolam does not restrict its short-term use for the approved indication.

The proposed implementation date for this decision was 1 January 2014.

Interim decision public submissions

Thirty-seven submissions were received. Six of those submissions were submissions that the delegate must take into consideration (submissions from members of the public who provided submissions during the pre-meeting consultation round). Five of those 6 submissions supported the delegate's interim decision.

Thirty-one submissions were submissions that they delegate may take into consideration (submissions from members of the public who did not provide submissions during the pre-meeting consultation round) and were considered. Of those 31 submissions, 28 supported the delegate's interim decision. Two submissions which supported the decision raised concerns that the implementation date of 1 January 2014 may not be achievable. One submission was received after the interim decision consultation round closed but was considered by the delegate.

Edited versions of these submissions are available at Public submissions on scheduling matters.

Delegates consideration

The delegate considered the following in regards to this proposal:

- scheduling proposal;
- public submissions received;
- the evaluation report (not publicly available);
- ACMS advice;
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[7];
- other relevant information.

[7] Scheduling Policy Framework for Medicines and Chemicals <http://www.tga.gov.au/industry/scheduling-spf.htm>

Delegates final decision

The delegate has reviewed the public submissions and other evidence and has confirmed the interim decision.

The delegate has made a final decision to amend the *Standard for the Uniform Scheduling of Medicines and Poisons* to include:

- The rescheduling of alprazolam from Schedule 4 to Schedule 8;
- A new entry in Appendix D, paragraph 5 for Benzodiazepine derivatives, including those separately specified in Schedule 4 and Schedule 8.

The delegate's final decision also includes the decision that the scheduling of the remaining benzodiazepines remains appropriate.

After reviewing the public submissions and in consultation with the States and Territories, the delegate has extended the implementation date to 1 February 2014.

The delegate has confirmed that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) the risks and benefits of the use of a substance, (b) the purposes for which a substance is to be used and the extent of use of a substance, (c) the toxicity of a substance, (d) the dosage, formulation, labelling, packaging and presentation of a substance and (e) the potential for abuse of a substance.

The delegate has confirmed that the reasons for the decision are in keeping with those for the interim decision as follows:

- Alprazolam has increased morbidity and mortality in overdose with possible increased toxicity. It does not appear to have any additional therapeutic benefits compared with any other substance in the class.
- There has also been a rapid increase in use of Alprazolam compared with other benzodiazepines and evidence of widespread misuse.
- Alprazolam - concerns of possible increased toxicity.
- Alprazolam - concern that current pack size is inappropriate for indications.
- There is evidence of abuse of Alprazolam and misuse with opiods with it being more subject to diversion from licit to illicit use.
- Listing in Schedule 8 of Alprazolam does not restrict its short-term use for the approved indication.

Schedule entry

Schedule 8 – New entry

ALPRAZOLAM.

Appendix D, Paragraph 5 – New entry

BENZODIAZEPINE DERIVATIVES, including those separately specified in Schedule 4 and Schedule 8.

2.2 Diclofenac

Scheduling proposal

The medicines scheduling delegate considered a proposal to exempt from scheduling diclofenac, when presented as a 140 mg or less diclofenac transdermal drug delivery system from the *Standard for the Uniform Scheduling of Medicines and Poisons*.

The delegate referred the proposal to the Advisory Committee on Medicines Scheduling (ACMS) for advice.

Scheduling history

In March 1981, diclofenac was included in Schedule 4.

In February 1997, the National Drugs and Poisons Schedule Committee (NDPSC) rescheduled from Schedule 4 to Schedule 2, dermal preparations (creams) containing 1 per cent or less of diclofenac. This decision was based on the safety profile of a 1 per cent formulation and the then approved indications for use in readily recognised conditions (minor pain relief), which did not include treatment of solar keratosis.

In August 1999, the NDPSC decided that the scheduling of diclofenac in dermal preparations remained appropriate after considering recommendations from the Trans-Tasman Harmonisation Working Party to exempt diclofenac for dermal use.

In November 1999, the NDPSC deferred consideration of the scheduling of diclofenac in dermal preparations.

In February 2000, the NDPSC exempted dermal preparations of diclofenac from scheduling based on additional safety data.

In March 2011, following advice from the December 2010 ACMS meeting, the delegate included dermal preparations containing more than 1 per cent of diclofenac or preparations for the treatment of solar keratosis in Schedule 4.

In February 2012, following advice from the October 2011 ACMS meeting, the delegate rescheduled dermal preparations containing more than 1 per cent up to 4 per cent or less of diclofenac, except when for the treatment of solar keratosis, to Schedule 2. The delegate also confirmed that Schedule 4 remained appropriate for preparations containing more than 4 per cent of diclofenac, that preparations containing 1 per cent or less of diclofenac would remain unscheduled and that preparations for use in solar keratosis would remain in Schedule 4.

In February 2013, following advice from the October 2012 ACMS meeting, the delegate included transdermal preparations for topical use containing 140 mg or less of diclofenac in Schedule 2, with an implementation date of 1 May 2013.

Current scheduling status

Diclofenac is currently included in Schedules 2, 3 and 4 and Appendices F and H.

Public pre-meeting submissions

Four public pre-meeting submissions were received.

Three did not support the proposal.

One indicated that it would have liked to comment on the proposed scheduling changes but felt that there was not information available regarding the proposal in order to comment.

The redacted public submissions are available at http://www.tga.gov.au/industry/scheduling-submissions.htm.

ACMS advice to the delegate

The ACMS recommended that the current scheduling of diclofenac remains appropriate.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the ACMS include (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The recommendation comprised of the following:

- there has been no clinical/marketing experience with this novel formulation in Australia; and
- Schedule 2 allows capacity to obtain professional advice from a pharmacist at the time of purchase.

Delegates interim decision

The delegate made an interim decision that the current scheduling of diclofenac remained appropriate, i.e. no change to the current scheduling.

The delegate decided that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* include (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The decision that the entry for diclofenac remains appropriate included the following reasons:

- there has been no clinical/marketing experience with this novel formulation in Australia; and
- Schedule 2 allows capacity to obtain professional advice from a pharmacist at the time of purchase.

Interim decision public submissions

No public submissions were received.

Delegates consideration

The delegate considered the following in regards to this proposal:

- scheduling proposal;
- public submissions received;
- the evaluation report (not publicly available);
- ACMS advice;
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[8];
- other relevant information.

Delegate final decision

The delegate has confirmed the interim decision as no public submissions or other evidence has been received to alter the interim decision.

[8] Scheduling Policy Framework for Medicines and Chemicals <http://www.tga.gov.au/industry/scheduling-spf.htm>

The delegate has made a final decision that the current scheduling of diclofenac remains appropriate, i.e. no change to the current scheduling.

The delegate has confirmed that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision as follows:

- there has been no clinical/marketing experience with this novel formulation in Australia; and
- Schedule 2 allows capacity to obtain professional advice from a pharmacist at the time of purchase.

2.3 Hydrocortisone & hydrocortisone acetate

Scheduling proposal

The medicines scheduling delegate considered a proposal to reschedule preparations containing 1 per cent or less of hydrocortisone and hydrocortisone acetate when combined with antifungal substances for dermal use from Schedule 3 to Schedule 2 in the *Standard for the Uniform Scheduling of Medicines and Poisons*.

The delegate referred the proposal to the Advisory Committee on Medicines Scheduling (ACMS) for advice.

Scheduling history

In May 1981, the Poisons Schedule Committee (PSC) confirmed that the scheduling of hydrocortisone remained appropriate, i.e. in Schedule 4. The PSC confirmed this position again in February 1982.

In August 1985, the PSC decided to reschedule to Schedule 3, 0.5% or less of hydrocortisone when present as the only therapeutically active substance.

In November 1988, the Drugs and Poisons Schedule Committee (DPSC) decided not to reschedule 1% or less of hydrocortisone to Schedule 3 on the basis of advice from the then Australian Drug Evaluation Committee (ADEC) that the product in question was pharmacologically more active than other brands of 1% hydrocortisone cream in causing vasoconstriction.

In May 1995, the National Drugs and Poisons Schedule Committee (NDPSC) considered an application to reschedule rectal preparations containing hydrocortisone and cinchocaine from Schedule 4 to Schedule 3. The NDPSC gave in-principle support to the scheduling proposal, pending further advice. A decision was subsequently made out–of-session to reschedule hydrocortisone and cinchocaine topical preparations for rectal use, from Schedule 4 to Schedule 3.

In February 1996, the NDPSC confirmed that the intent of the May 1995 decision was to allow preparations containing 0.5% or less of hydrocortisone (alone or in combination with cinchocaine) to be available for rectal use (internal and externally) in both the ointment and suppository form, as Schedule 3.

In August 1998, the NDPSC decided not to list hydrocortisone and cinchocaine rectal preparations in Appendix H. This decision was primarily on the grounds that the incidence of misdiagnosis of fungal infections may be increased.

In February 1999, the NDPSC decided to reschedule hydrocortisone and hydrocortisone acetate (for dermal use containing 0.5% or less of hydrocortisone in packs containing 30 g or less of such

preparation, with no other therapeutically active substance or an antifungal as the only other therapeutically active substance), to Schedule 2. The Schedule 3 entry was also amended to include a specific reference to suppositories.

In May 1999, the NDPSC decided to include hydrocortisone in preparations for rectal use in Appendix H. This decision was based on controls on advertising and that the Therapeutic Good Advertising Council allows advertising of haemorrhoid treatments, provided there are statements limiting the nature of the relief; that advertising of both Schedule 2 and Schedule 3 products will enable pharmacists to offer comparative professional advice; and the issue of possible systemic absorption would be addressed through pharmacist counselling.

In November 2001, the NDPSC considered the scheduling of products containing hydrocortisone and hydrocortisone acetate, with astringents as active ingredients, for rectal use. The NDPSC decided to amend the scheduling of hydrocortisone and hydrocortisone acetate to exempt unscheduled astringents and restore the product to Schedule 3. The NDPSC considered that the presence of aluminium acetate and zinc oxide the product, whilst therapeutically active, were there primarily for their astringent effects rather than for systemic effects.

In June 2002 the NDPSC decided not to include hydrocortisone for dermal use in Appendix H. However, in response to post-meeting comment, the October 2002 NDPSC reconsidered this scheduling proposal and decided to include hydrocortisone for dermal use in Appendix H.

In October 2005, the NDPSC considered an application for the rescheduling of hydrocortisone acetate (in combination with an anaesthetic) for rectal use from Schedule 3 to Schedule 2. The NDPSC decided that the scheduling of hydrocortisone remained appropriate. This decision was based on concerns that consumers may sometimes have difficulty in differentiating between haemorrhoids and other conditions for which the use of a corticosteroid would be inappropriate; that if used on infected skin, there was potential for any infection to be masked or exacerbated; and concern that the safety data presented as part of the rescheduling application did not truly reflect the safety of the product for anorectal use as it included all adverse events relating to hydrocortisone, regardless of route, dose or duration of treatment.

In June 2006, the NDPSC reconsidered an application to reschedule hydrocortisone acetate (in combination with an anaesthetic) for rectal use. After due consideration of the new safety data presented, the NDPSC decided that the current scheduling of hydrocortisone and hydrocortisone acetate remained appropriate. The applicant had again not adequately justified exactly what advantage there would be to the consumer, should this product be down scheduled and therefore accessed without mandatory intervention of the pharmacist.

In February 2007, the NDPSC decided to reschedule hydrocortisone 0.5% in combination with an anaesthetic for rectal use from Schedule 3 to Schedule 2 to harmonise with New Zealand.

In June 2007, the NDPSC decided to amend the Schedule 2 and 3 entries to only capture human use. This was a result of a decision to vary the February 2007 decision to capture all veterinary use in Schedule 4.

In October 2007, the NDPSC decided to correct the wording of the Schedule 2 entry for hydrocortisone to specify human rectal use, in line with the decision of the June 2007 NDPSC meeting.

In June 2008, the NDPSC decided to include hydrocortisone in Appendix F, Part 3, with warning statements 38, 72, 73, 74 and 75 (for dermal use when included in Schedule 2 or 3), and warning statements 38 & 75 (for topical rectal use when included in Schedule 2 or 3).

Current scheduling status

Hydrocortisone is currently included in Schedules 2, 3 and 4 and Appendices F and H. Hydrocortisone acetate is included in Schedules 2 and 3.

Public pre-meeting submissions

Four public pre-meeting submissions were received. One supported the scheduling proposal. Three did not support the scheduling proposal.

The redacted public submissions are available at http://www.tga.gov.au/industry/scheduling-submissions.htm.

ACMS advice to the delegate

The ACMS recommended that the current scheduling of hydrocortisone and hydrocortisone acetate remains appropriate.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the ACMS include (a) the risks and benefits of the use of a substance.

The reason for the recommendation comprised of the following:

- This product contains an increased concentration of hydrocortisone. Therefore, there are increased risks of:
  - masking symptoms, particularly in children, which can be mitigated by mandatory pharmacist intervention;
  - exacerbation of bacterial infections through inappropriate application;
  - inappropriate use with a higher concentration, with no demonstrated increase in benefit were it to be down-scheduled.

Delegates interim decision

The delegate made an interim decision that the current scheduling of hydrocortisone and hydrocortisone acetate remained appropriate, i.e. no change to the current scheduling.

The delegate decided that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* include (a) the risks and benefits of a substance.

The decision that the entry for hydrocortisone and hydrocortisone acetate remains appropriate included the following reasons:

- This product contains an increased concentration of hydrocortisone. Therefore, there are increased risks of:
  - masking symptoms, particularly in children, which can be mitigated by mandatory pharmacist intervention;
  - exacerbation of bacterial infections through inappropriate application;
  - inappropriate use with a higher concentration, with no demonstrated increase in benefit were it to be down-scheduled.

Interim decision public submissions

No public submissions were received.

Delegates consideration

The delegate considered the following in regards to this proposal:

- scheduling proposal;
- public submissions received;
- the evaluation report (not publicly available);
- ACMS advice;
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[9];
- other relevant information.

Delegate final decision

The delegate has confirmed the interim decision as no public submissions or other evidence has been received to alter the interim decision.

The delegate has made a final decision that the current scheduling of hydrocortisone and hydrocortisone acetate remains appropriate, i.e. no change to the current scheduling.

The delegate has confirmed that the relevant matters under subsection 52E(1) of the T*herapeutic Goods Act 1989* are (a) the risks and benefits of a substance.

The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision as follows:

- This product contains an increased concentration of hydrocortisone. Therefore, there are increased risks of:
  - masking symptoms, particularly in children, which can be mitigated by mandatory pharmacist intervention;
  - exacerbation of bacterial infections through inappropriate application;
  - inappropriate use with a higher concentration, with no demonstrated increase in benefit were it to be down-scheduled.

2.4 Lisdexamfetamine

Scheduling proposal

The medicines scheduling delegate considered a proposal to include lisdexamfetamine in Schedule 8 in the *Standard for the Uniform Scheduling of Medicines and Poisons*.

The delegate referred the proposal to the Advisory Committee on Medicines Scheduling (ACMS) for advice.

Scheduling history

There is no scheduling history for lisdexamfetamine as is it not currently scheduled.

[9] Scheduling Policy Framework for Medicines and Chemicals <http://www.tga.gov.au/industry/scheduling-spf.htm>

Current scheduling status

Lisdexamfetamine is not scheduled.

Public pre-meeting submissions

One public pre-meeting submission was received, which supported the proposal.

The redacted public submissions are available at http://www.tga.gov.au/industry/scheduling-submissions.htm.

ACMS advice to the delegate

The ACMS recommended that lisdexamfetamine be listed under Schedule 8.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the ACMS include: (a) the risks and benefits of the use of a substance, and (e) the potential for abuse.

The reasons for the recommendation comprised of the following:

- On account of its long acting characteristics, it is useful and convenient for the treatment of ADHD, but it does carry all the risks of the amphetamines.
- Amphetamines are well established as substances of abuse which warrant inclusion in Schedule 8.

Delegates interim decision

The delegate made an interim decision to include lisdexamfetamine in Schedule 8. The proposed implementation date for this decision was 1 September 2013.

The delegate decided that the relevant matters under section 52E (1) of the T*herapeutic Goods Act 1989* include (a) the risks and benefits of a substance and (e) the potential for abuse of a substance.

Interim decision public submissions

No public submissions were received.

Delegates consideration

The delegate considered the following in regards to this proposal:

- scheduling proposal;
- public submissions received;
- ACMS advice;
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[10];
- other relevant information.

Delegate final decision

The delegate has confirmed the interim decision as no public submissions or other evidence has been received to alter the interim decision.

[10] Scheduling Policy Framework for Medicines and Chemicals <http://www.tga.gov.au/industry/scheduling-spf.htm>

The delegate has made a final decision to amend the *Standard for the Uniform Scheduling of Medicines and Poisons* to include lisdexamefamine in Schedule 8.

The delegate has confirmed the implementation date of 1 September 2013.

The delegate has confirmed that the relevant matters under subsection52E(1) of the *Therapeutic Goods Act 1989* are ((a) the risks and benefits of the use of a substance, and (e) the potential for abuse.

The delegate has confirmed that the reasons for the decision to include lisdexamfetamine in Schedule 8 are in keeping with those for the interim decision, as follows:

- On account of its long acting characteristics, it is useful and convenient for the treatment of ADHD, but it does carry all the risks of the amphetamines.
- Amphetamines are well established as substances of abuse which warrant inclusion in Schedule 8.

Schedule entry

Schedule 8 – New entry

LISDEXAMFETAMINE.

2.5 Nabiximols

Scheduling proposal

The medicines scheduling delegate considered a proposal to reschedule Nabiximols (Sativex®) from Paragraph 3 of Appendix D to Paragraph 1 of Appendix D in the *Standard for the Uniform Scheduling of Medicines and Poisons*.

The delegate referred the proposal to the Advisory Committee on Medicines Scheduling (ACMS) for advice.

Scheduling history

In October 2009, the committee considered an entry specific for *Cannabis sativa* extract, Nabiximols, after the issue that certain jurisdictions were unable to allow SAS access to the substance as it was captured under Schedule 9 was raised in the June 2009 meeting. As discussed in June, the Committee members agreed on the Schedule 8 listing. The Committee also agreed that the Schedule 8 entry should limit the allowed presentation to buccal sprays as this would further reinforce the very restricted scope of this entry and would require any new presentation to be brought to the attention of the Committee.

In May 2010, Nabiximols were included in Schedule 8 and Appendices D and K.

The committee advised that Nabiximols needed to be added to Appendix D, paragraph 3 to limit access through SAS Category A. This addition would allow restricted access to Nabiximols only, not to cannabis extracts but would not prohibit use for clinical trials provided by an authorised prescriber only. The Committee agreed to not restrict the Schedule 8 Nabiximols entry by indication (for Multiple Sclerosis).

Members additionally agreed that it would be appropriate to include Nabiximols in Appendix K due to sedating effects.

Current scheduling status

Nabiximols are included in Schedule 8, Appendix D and Appendix K.

Nabiximols is defined with the *Standard for the Uniform Scheduling of Medicines and Poisons* as "botanical extract of *Cannabis sativa*, which includes the following cannabinoids: tetrahydrocannabinol, cannabidiol, cannabinol, cannabigerol, cannabichromene, cannabidiolic acid, tetrahydrocannabinolic acid, tetrahydrocannabivarol, and cannabidivarol, where tetrahydrocannabinol and cannabidiol (in approximately equal proportions) comprise not less than 90 per cent of the total cannabinoid content) in a buccal spray for human therapeutic use".

Public pre-meeting submissions

Eight public pre-meeting submissions were received addressing the proposal to reschedule Nabiximols from Paragraph 3 of Appendix D to Paragraph 1 of the same appendix. All 8 submissions supported the proposal.

The redacted public submissions are available at http://www.tga.gov.au/industry/scheduling-submissions.htm.

ACMS advice to the delegate

The ACMS recommended that paragraph 1 of Appendix D be amended to include the entry of Nabiximols.

The proposed implementation date for this decision is 1 September 2013.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included (a) the risks and benefits of the use of a substance.

The reasons for the recommendation comprised of the following:

- Specialist oversight is required for safe prescribing of the drug and an entry in Appendix D paragraph 1 is consistent with TGA's decision with respect to specialist prescribers for the current registered products.

Delegates interim decision

The delegate made an interim decision to reschedule nabiximols from Paragraph 3 of Appendix D to Paragraph 1 of Appendix D. The proposed implementation date for this decision was 1 September 2013.

The delegate decided that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* include (a) the risks and benefits of a substance.

The decision that the Appendix D entry for nabiximols be amended included the following reasons:

- Appendix D, paragraph 1, is for medicines approved on the ARTG for use in Australia whereas Appendix D, paragraph 3, is for medicines that are not included in the ARTG and thus not approved for use in Australia.
- One product containing nabiximols has been approved for use in Australia and is included on the ARTG.
- Specialist oversight is require for safe prescribing of the drug and an entry in Appendix D paragraph 1 is consistent with TGA's decision with respect to specialist prescribers for the current registered products.

Interim decision public submissions

No public submissions were received.

Delegates consideration

The delegate considered the following in regards to this proposal:

- scheduling proposal;
- public submissions received;
- ACMS advice;
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[11];
- other relevant information.

Delegate final decision

The delegate has confirmed the interim decision as no public submissions or other evidence has been received to alter the interim decision.

The delegate has made a final decision to amend the Standard for the Uniform Scheduling of Medicines and Poisons to reschedule nabiximols from Paragraph 3 of Appendix D to Paragraph 1 of Appendix D.

The delegate has confirmed the implementation date of 1 September 2013.

The delegate has confirmed that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) the risks and benefits of the use of a substance.

The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision, as follows:

- Appendix D, paragraph 1, is for medicines approved on the ARTG for use in Australia whereas Appendix D, paragraph 3, is for medicines that are not included in the ARTG and thus not approved for use in Australia.
- One product containing nabiximols has been approved for use in Australia and is included on the ARTG.
- Specialist oversight is require for safe prescribing of the drug and an entry in Appendix D paragraph 1 is consistent with TGA's decision with respect to specialist prescribers for the current registered products.

Schedule entry

Appendix D, Paragraph 3 – Amendment

NABIXIMOLS – Delete entry

Appendix D, Paragraph 1 – New entry

NABIXIMOLS.

[11] Scheduling Policy Framework for Medicines and Chemicals <http://www.tga.gov.au/industry/scheduling-spf.htm>

2.6 Oseltamivir

Scheduling proposal

The medicines scheduling delegate considered a proposal to reschedule oseltamivir for the treatment and prevention of influenza type A and type B from Schedule 4 to Schedule 3 in the *Standard for the Uniform Scheduling of Medicines and Poisons*.

The delegate referred the proposal to the Advisory Committee on Medicines Scheduling (ACMS) for advice.

Scheduling history

In November 2000, the National Drugs and Poisons Schedule Committee (NDPSC) decided to include oseltamivir in Schedule 4 following a recommendation made by the then Australian Drug Evaluation Committee (ADEC) to register a new drug application for Tamiflu® capsules, containing 75 mg of oseltamivir phosphate, for the treatment of infections due to influenza A and B viruses in adults and children aged twelve years and older.

In October 2004, the NDPSC considered an application to reschedule oseltamivir from Schedule 4 to Schedule 3, and for inclusion in Appendix H. The NDPSC deferred making a decision to allow input by the National Influenza Pandemic Action Committee (NIPAC). The NDPSC considered the available data to be inadequate in providing a reassurance that widening the availability of oseltamivir for the treatment of influenza through inclusion in Schedule 3 would not facilitate the spread of resistance to neuraminidase inhibitor (NI) class of drugs. The NDPSC also considered it important to its consideration if advice was received from authorities that deal with communicable diseases to gain an understanding of the implications a Schedule 3 availability of oseltamivir for the treatment of influenza would have on the national strategies for managing influenza epidemics or pandemics.

In October 2005, following receipt of advice from the National Influenza Pandemic Action Committee (NIPAC), the NDPSC reconsidered a proposal to reschedule oseltamivir from Schedule 4 to Schedule 3, and for inclusion in Appendix H. The NDPSC decided that the scheduling of oseltamivir remained appropriate. This decision was based on concerns regarding the likelihood of correct diagnosis by pharmacists without accurate point-of-care tests or physical examination during non-pandemic periods and concerns raised in regard to the then available inconclusive data relating to the likelihood of the development of resistance. In line with these concerns, the NDPSC acknowledged the need for the continued gathering of epidemiological data in relation to prevalence/resistance of influenza, which would be logistically difficult if oseltamivir was down-scheduled to Schedule 3. The NDPSC wanted to see possible arrangements explored for appropriate access to oseltamivir should either a localised outbreak or an influenza pandemic occur.

In February 2006, following suggestion for rapid access to oseltamivir in extenuating circumstances, the NDPSC noted the legislative powers that exist at State and Territory level as well as activity at the Commonwealth level which would facilitate the supply of a Schedule 4 substance (such as oseltamivir) without a prescription during either a localised outbreak or an influenza pandemic.

In October 2006, the NDPSC considered a request from the New Zealand Medicines Classification Committee (NZ MCC) to harmonise the scheduling of oseltamivir with NZ. The NDPSC agreed that Australia was harmonised with NZ on the scheduling of oseltamivir given that the only change to the NZ classification was an exemption to do with supply of the medication and that such mechanisms of supply set down by jurisdictions had been duly explored at the February 2006 NDPSC meeting. Thus the NDPSC concluded that the scheduling of oseltamivir remained appropriate.

In October 2008, the NDPSC considered an application to reschedule oseltamivir from Schedule 4 to Schedule 3. The NDPSC decided that the scheduling of oseltamivir remained appropriate. The NDPSC remained concerned about the risk of the development of resistance, and that down-scheduling could potentially lower influenza vaccination rates, including among vulnerable patient groups. The NDPSC also noted that without appropriate physical examination the risk of misdiagnosis could lead to delays in treatment and potential exposure to adverse effects without the prospect of a significant benefit. The NDPSC expressed confidence that all States and Territories had established, or were planning to establish, mechanisms to facilitate rapid access to oseltamivir should circumstances warrant.

Current scheduling status

Oseltamivir is included in Schedule 4

Public pre-meeting submissions

Four public pre-meeting submissions were received.

Two submissions supported the proposal; one submission did not support the proposal; one submission indicated that while rescheduling has the potential to improve timely access to oseltamivir, there are concerns which may outweigh the benefit.

The redacted public submissions are available at http://www.tga.gov.au/industry/scheduling-submissions.htm.

ACMS advice to the delegate

The ACMS recommended that the current scheduling of oseltamivir remains appropriate.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the ACMS include: (a) the risks and benefits of the use of a substance, and (f) other matters considered necessary to protect public health.

The reasons for the recommendation comprise of the following:

- Concern about the potential for increased resistance with widespread use.
- Concern about misdiagnosis in the context that a doctor would be able to follow-up laboratory tests and improve surveillance.
- Risk of reduced level of laboratory surveillance of influenza in the absence of medical prescribing.
- Arrangements exist within the jurisdictions for access to oseltamivir during influenza pandemic situations.

Delegates interim decision

The delegate made an interim decision that the current scheduling of oseltamivir remained appropriate, i.e. no change to the current scheduling.

The delegate decided that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* include (a) the risks and benefits of a substance and (f) any other matters that the Secretary considers necessary to protect public health.

The decision that the entry for oseltamivir remains appropriate as a Schedule 4 listing included the following reasons:

- agreement with the ACMS reasoning outlined above;

- the potential for increased resistance;
- the potential for misdiagnosis; and
- the potential for decreased laboratory surveillance in the absence of medical prescribing.

Interim decision public submissions

No public submissions were received.

Delegates consideration

The delegate considered the following in regards to this proposal:

- scheduling proposal;
- public submissions received;
- the evaluation report (not publicly available);
- ACMS advice;
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[12];
- other relevant information.

Delegates final decision

The delegate has confirmed the interim decision as no public submissions or other evidence has been received to alter the interim decision.

The delegate has made a final decision that the current scheduling of oseltamivir remains appropriate, i.e. no change to the current scheduling.

The delegate has confirmed that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) the risks and benefits of a substance and (f) any other matters that the Secretary considers necessary to protect public health.

The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision, as follows:

- Concern about the potential for increased resistance with widespread use.
- Concern about misdiagnosis in the context that a doctor would be able to follow-up laboratory tests and improve surveillance.
- Risk of reduced level of laboratory surveillance of influenza in the absence of medical prescribing.
- Arrangements exist within the jurisdictions for access to oseltamivir during influenza pandemic situations.

[12] Scheduling Policy Framework for Medicines and Chemicals <http://www.tga.gov.au/industry/scheduling-spf.htm>

3. Scheduling proposals referred to the March 2013 joint meeting of the Advisory Committee on Chemicals Scheduling and Advisory Committee on Medicines Scheduling (ACCS-ACMS#5)

3.1 Adrenaline, Bupivacaine and Lignocaine

Scheduling proposal

The Chemicals Scheduling Delegate and the Medicines Scheduling Delegate (the delegates) considered a proposal to reschedule a veterinary preparation containing adrenaline, bupivacaine and lignocaine from Schedule 4 to Schedule 6 in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).

The delegates referred the proposal to the Advisory Committee on Chemicals Scheduling (ACCS) and the Advisory Committee on Medicines Scheduling (ACMS) for advice.

Adrenaline, bupivacaine and lignocaine are listed in Schedule 4. Adrenaline and lignocaine, apart from the listing in Schedule 4, are also listed in Schedules 3 and 2 respectively.

Scheduling history

Adrenaline

In January 1955, the Poisons Schedules Committee (PSC) listed adrenaline in Schedules 2 and 3 for preparations of less than 1 per cent and in Schedule 4 for preparations containing more than 1 per cent.

In May 1956, the PSC decided that the Schedule 2 entry was deleted and the Schedule 3 entry refined to exempt concentrations of less than 0.01 per cent.

In August 1985, the PSC decided to amend the Schedule 3 and 4 entries for adrenaline to raise the exemption to preparations containing 0.02 per cent, stating that such a low level is not toxic and does not pose a health risk except in diabetics.

In February 1999, the National Drugs and Poisons Schedule Committee (NDPSC) recommended that New Zealand harmonise with the Australian adrenaline scheduling. New Zealand subsequently agreed to this recommendation.

In February 2010, the NDPSC considered an application to include adrenaline auto-injector in Appendix H entry. The NDPSC agreed that auto-injectors were included in Schedule 3 to facilitate emergency access for a specific group of people rather than the usual purpose of the majority of Schedule 3 listings i.e. to provide the community with access to a beneficial therapeutic option which requires professional advice but not a prescription. The NDPSC agreed that it was concerned that advertising could undermine this distinction. The NDPSC decided that the inclusion of adrenaline in Appendix H was inappropriate.

Bupivacaine

In 1983 August, the PSC decided to include bupivacaine in Schedule 4 of the SUSMP.

Lignocaine

In February 1998, the NDPSC considered a submission for rescheduling of dermal preparations containing 1 per cent or less of lignocaine in packs of 30 g or less, from Schedule 2 to unscheduled. The NDPSC decided that based on the use pattern at that time, it did not wish to amend the scheduling of lignocaine.

In May 1998, following its reconsideration of the applicant's comments, and subsequent examination of public comments, the NDPSC decided that it did not wish to change the decision of the February 1998 Meeting and that lignocaine would remain a scheduled substance.

In October 2008, the NDPSC considered a proposal to broaden the current Schedule 2 exemption for dermal use (less than or equal to 2 per cent) to also exempt use on gums.

At that time the NDPSC decided that the current Scheduling remained appropriate.

The Trans-Tasman Harmonisation Working Party recommended that 2 per cent lignocaine or less in dermal preparations should be exempted from scheduling. This recommendation was adopted at the February 2001 NDPSC Meeting.

Public pre-meeting submissions

Five public submissions (including a late submission) were received.

Two submissions (both have identical contents) indicated that inclusion of these substances in Schedule 6 could potentially lead to an increase in adoption of the use of these substances for mulesing, ultimately leading to improve welfare outcomes for lambs undergoing mulesing. These two submissions supported the scheduling proposal to reschedule these substances.

One submission indicated that it supported the rescheduling of adrenaline and lignocaine. The submission did not provide comments on bupivacaine.

One submission indicated that rescheduling these substances would potentially leads to misuse, including for treating castration wounds and injuries, therefore did not support the delegates' proposal.

One late public submission indicated that it did not oppose the delegates' rescheduling proposal, provided it does not result in Tri-solfen no longer being available to woolgrowers for the purpose of alleviating the pain associated with the mulesing procedure and as long as the scheduling requirements ensure that the product continues to be used in the manner intended and described on the product label.

The redacted public submissions are available at http://www.tga.gov.au/industry/scheduling-submissions-1303.htm.

Advisory Committee on Chemicals Scheduling (ACCS) and the Advisory Committee On Medicines Scheduling (ACMS) advice to the delegates

The joint ACCS & ACMS Committee recommends that the current scheduling of adrenaline, bupivacaine and lignocaine remains appropriate.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included; (a) the risks and benefits of the use of a substance, (c) the toxicity of a substance and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The following reasons were noted:

- insufficient data available to demonstrate that a change in Schedule will result in wider appropriate usage versus wider inappropriate usage.
- as mulesing is a regulated process, there is no evidence that rescheduling would improve the extent of use.
- rescheduling would increase the risk of the product being inappropriately used.

- rescheduling would increase the likelihood of larger quantities being available which could lead to misuse.

Delegates interim decision

The delegates considered, and accepted, the advice of the joint ACCS & ACMS, advising that the specific uses of the veterinary product for pain relief in the practice of 'mulesing' sheep require veterinary supervision, and that changes to the existing Schedule 4 entries of the three active ingredients are not warranted. Accordingly, no scheduling changes are proposed in making an interim decision.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included; (b) the purpose, (c) the toxicity of a substance, (d) the dosage, formulation, labelling, packaging and presentation of a substance, (e) the potential for abuse and (f) any other matters.

The following reasons were noted:

- as mulesing is a regulated process, there is no evidence that rescheduling would improve the extent of use.
- the toxicity of the local anaesthetic ingredients and the relatively narrow window of effectiveness in pain relief associated with mulesing, warrant appropriate supervision of treatment by a veterinarian.
- rescheduling to Schedule 6 could result in the product, currently available in 100 ml injection vials, being made available in much larger bulk containers, increasing the risk of inappropriate use.
- rescheduling from Schedule 4 to Schedule 6 could increase the risk of the product being inappropriately used for purposes other than pair relief after mulesing.
- a broadening of use in pain relief for the practice of mulesing is a desirable outcome, but this can be achieved within existing scheduling arrangements, especially via advertising, which would remain restricted to professional journals and related sources.

Submissions on interim decision

Six submissions were received. Only one of the submissions was a valid submission. Other submissions were submissions from parties other than those who made a valid submission in response to the original invitation or the applicant.

Two submissions indicated that mulesing does not require diagnosis or the attendance of a veterinarian. The product containing substances alleviate pain in lambs undergoing mulesing and this process does not require direct (on farm) veterinary supervision or monitoring. The submissions therefore support the applicant’s proposal to rescheduling of the substances in the product.

One submission indicated that under the Victorian Drugs and Poisons Controlled Substances Regulation, before dispensing a product the veterinary practitioner must ensure that the drug or poison is for the treatment of an animal under the veterinarian’s care. Most private veterinary practitioners rarely visit commercial sheep farm. The submission noted that it would be advantageous from an animal ethics view point if all mulesed lambs were treated with this product. This could be achieved if the product was not listed in Schedule 4 and could be advertised more generally.

One submission noted that move to make the product containing these substances more readily available to woolgrowers is likely to result in an improved animal health outcome.

Two submissions noted that for those lambs that require the mulesing procedure, the use of the product as a post-operative analgesic provides the best welfare outcome currently available to producers. Adoption of practices to support sheep welfare is of critical importance to the sustainability of the Australian wool-production industry. The submissions noted that the proposed scheduling change would result in a significant increase in use of the product for its intended purpose by improving its availability to sheep producers and allowing the direct promotion of the product to end-users. The submissions indicated that the preparations for mulesing that contain adrenaline, bupivacaine and lignocaine be listed in Schedule 6.

The redacted public submissions are available at http://www.tga.gov.au/industry/scheduling-submissions.htm.

Delegate's consideration

The delegate considered the following in regards to this proposal:

- scheduling proposal;
- ACCS & ACMS advice;
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[13];
- public submissions; and
- other relevant information.

Delegate's final decision

The delegates have considered the submissions received following publication of the interim decision to retain Schedule 4 status for this product, in addition to a further review of the initial submissions and the advice from the ACCS &ACMS. On the basis of this review, the delegates have decided to set aside the interim decision, and institute scheduling changes that would allow the specific product under consideration to be re-scheduled to Schedule 5.

The proposed implementation date for this decision is 1 February 2014.

Other reasons

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegates included; (a) the risks and benefits of the use of the substance, (b) the purpose, (c) the toxicity of a substance, (d) the dosage, formulation, labelling, packaging and presentation of a substance, and (e) the potential for abuse.

The principal reason behind the interim decision to retain the two local anaesthetic active ingredients lignocaine and bupivacaine) in Schedule 4 was advice tendered by the ACCS & ACMS and in the Australian Pesticides and Veterinary Medicines Authority (APVMA) submission, that 'mulesing' is a procedure that should be carried out under the supervision of a veterinarian. This was alleged to be necessary to ensure appropriate treatment, including observance of the 90-day withholding period prior to slaughter for meat consumption. This advice further contended that re-scheduling from Schedule 4 could lead to inappropriate use (for treatment of wounds other than

[13] Scheduling Policy Framework for Medicines and Chemicals <http://www.tga.gov.au/industry/scheduling-spf.htm>

those associated with ‘mulesing’) and an increase in the availability of the product in larger containers.

All these points were effectively rebutted in the post-decision submissions, one of which came from the original applicant, one from the product developer, one from the product registrant, and three from agricultural and woolgrowing authorities. In particular, the delegates now note that information about the product being supplied in 100mL containers is erroneous, and that it is currently available in containers from 1 to 22L in size. In relation to main points raised in the submissions, the delegates are now of the opinion that the requirement for veterinary intervention and/or supervision is not needed for the proper conduct of ‘mulesing’. The evidence tendered suggests that the current practice, with farmers and contractors using the product without direct veterinary supervision has been working well, with no evidence of inappropriate use. Furthermore, the delegates accept the contention that a requirement for veterinary prescription can place an undue burden on farmers and contractors working in areas remote from the availability of veterinary practices. Re-scheduling would be reasonably expected to result in an improvement in animal welfare, with more sheep being treated to reduce pain and infection than would otherwise have been left untreated.

The issue then becomes what scheduling change best meets this objective. The original and supporting submissions propose re-scheduling to Schedule 6, on the ‘cascading’ principle of easing schedule requirements, although there was some comment that Schedule 5 could also be an appropriate level of scheduling. In 1994-96, the then NDPSC considered the issue of whether the active components of veterinary medicines included in Schedule 6 should be re-scheduled, where possible, to Schedule 5. This was driven by a concern that medicines intended for the oral treatment of animals could be inappropriately labelled with the signal heading POISON, rather than the previously available signal heading of CAUTION. A number of veterinary medicines were re-scheduled to Schedule 5 where their toxicity profiles had been re-evaluated, including consideration of the likelihood that a child could reasonably be exposed to a fatal dose.

The product currently under consideration for re-scheduling contains lignocaine (4.06 per cent) and bupivacaine (0.42 per cent). At these dilutions, the acute toxicity profile is reasonably consistent with the Scheduling Policy Framework guidelines for listing in Schedule 5. Furthermore, the product label includes appropriate warning statements and safety directions to ensure that users are warned of the potential risks. It is also noted that lignocaine is available ‘over-the-counter in pharmacies’ (Schedule 2) in topical human medicines at concentrations up to 10 per cent, with exemption from scheduling at 2 per cent. This further reinforces the view that a POISON signal heading for a product intended for topical application with twice the exempt concentration of lignocaine appears to be unnecessary.

The other active ingredients in the product are adrenaline (0.0025 per cent) and the quaternary ammonium antiseptic (cetrimide 0.5 per cent). At these concentrations, both components are exempt from scheduling, and no adjustment needs to be made to their current SUSMP entries.

The delegates note that, currently, the APVMA has registered only one veterinary product containing bupivacaine while there are 14 products containing lignocaine (mostly in Schedule 4). It is therefore important that the re-scheduling of these actives to Schedule 5 should apply only to the particular product and its use in ‘mulesing’.

Schedule entry

Schedule 4 – Amendment

BUPIVACAINE **except** when included in Schedule 5.

Schedule 5 – New entry

BUPIVACAINE in aqueous gel preparations containing 0.5 per cent or less of bupivacaine, for the dermal spray-on treatment of wounds associated with 'mulesing' of sheep.

Schedule 4 – Amendment

LIGNOCAINE **except:**

(a) when included in Schedules 2 or 5;
(b) in dermal preparations containing 2 per cent or less of total local anaesthetic substances per dosage unit; or
(c) in lozenges containing 30 mg or less of total anaesthetic substances per dosage unit

Schedule 5 – New entry

LIGNOCAINE in aqueous gel preparations containing 4.5 per cent or less of lignocaine, for the dermal spray-on treatment of wounds associated with 'mulesing' of sheep.

3.2 Tylosin

Scheduling proposal

The Chemicals Scheduling Delegate and the Medicines Scheduling Delegate (the delegates) considered a proposal to reschedule tylosin from Schedule 5 to Schedule 4 in the *Standard for the Uniform Scheduling of Medicines and Poisons*.

The delegates referred the proposal to the Advisory Committee on Chemicals Scheduling (ACCS) and the Advisory Committee on Medicines Scheduling (ACMS) for advice.

Scheduling status

Tylosin is listed in Schedules 4 and 5.

Tylosin is a macrolide antimicrobial agent approved in Australia by the APVMA for use in poultry, pigs and cattle. As of March 2013, tylosin is available as an injection, water-soluble antimicrobial preparation and as premix. While injectable and water-soluble formulations are in Schedule 4 (Prescription Animal Remedy), the feed premix formulations are, according to the concentration of tylosin in the marketed premix, either in Schedule 4 or in Schedule 5 (available over-the-counter without a prescription).

Scheduling history

In November 1968, the then Poisons Schedule Sub-Committee (PSSC) recommended that an entry group 'antibiotics' be included in Schedule 4 except when tylosin and other macrolides bacitracin, erythromycin and oleandomycin when added to animal feedstuffs for the purpose of growth promotion in concentrations not exceeding 50 ppm, which should be exempt from scheduling. Antibiotic premixes for growth promotion purposes containing the antibiotics above in concentrations greater than 50 ppm but not in excess of 20,000 ppm should be exempt from Schedule 4 when packed and labelled in accordance with Schedule 6 of the Uniform Poisons Schedules. Water soluble antibiotic preparations intended for addition to animals' drinking water should not be made available without prescription.

In May 1977, the then Poisons Schedule Committee (PSC) decided to amend the Schedule 4 entry for antibiotics to include animal feedstuffs containing bacitracin, erythromycin, oleandomycin, tylosin and virginiamycin in concentration of 50 ppm or less of the total active antibiotic principles.

The PSC was of the opinion that the continued use of antibiotics as growth promotions in animal feedstuffs could lead to an impairment of their efficacy in the treatment of human disease.

In May 1978 specific entries for antibiotics including tylosin, bacitracin, erythromycin, oleandomycin and virginiamycin were included in Schedule 4, except in animal feedstuffs for growth promotion in concentrations of 50 mg / kg or less of the total active antibiotic principle (remained Schedule 6).

In November 1986, the then Drugs and Poisons Schedule Standing Committee (DPSSC) considered a submission to remove tylosin from Schedule 4 to Schedule 6. The review noted that if the concentration of tylosin in the premix was increased it would increase the chance of erythromycin resistance occurring in possible human pathogens. The DPSSC decided not to remove the Schedule 4 entry and recommended the Schedule 6 level of tylosin in premixes be increased from 2 to 5 per cent.

In November 1990, the DPSC considered an apparent anomaly in the scheduling of tylosin. The DPSC confirmed the current scheduling that the Schedule 4 entry related to uses involving therapeutic claims while Schedule 6 entry was solely for growth promotion purposes.

In May 1993, the DPSC decided to include safety directions for a Schedule 6 tylosin stockfeed premix.

In February 1996, the National Drugs and Poisons Schedule Committee (NDPSC) decided to reschedule tylosin from Schedule 6 to Schedule 5. The NDPSC considered that the registered products for oral use fell within the acute oral criteria of the new draft guidelines for Schedule 5 and recommended that tylosin when in veterinary products for oral use should be classified as Schedule 5.

In 1999, the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR) recommended "that all antibiotics for use in humans and animals (including fish) be classified as Schedule 4 (prescription only)." The JETACAR report also recommended that a review of the macrolides (tylosin, kitasamycin, oleandomycin) be undertaken as a priority to assess efficacy and to ensure that continued use is "not likely to impair the efficacy of any other prescribed therapeutic antibiotic or antibiotics for animal or human infections through the development of resistant strains of organisms".

In February 2003, the NDPSC scheduled / rescheduled all antibiotics (except tylosin, kitasamycin, oleandomycin) for use in human and animals in Schedule 4: viginiamycin, bacitracin, cuprimyxin, erythromycin, hygromycin, nalidixic acid, nisin, spiramycin and avoparcin as part of its response to the recommendations (in 1999) of the JETACAR.

The October 2003 NDPSC meeting considered a letter sent to feed mill sales representatives from XXXXX in which the company highlighted the Committee's decision regarding the rescheduling of virginiamycin to Schedule 4. XXXXX letter mentioned that XXXXX (containing tylosin) remained in Schedule 5 and was unaffected by the NDPSC decision. The NDPSC agreed to refer claims of inappropriate promotion of antibiotics that are yet to be reviewed under JETACAR to Expert Advisory Group on Antimicrobial Resistance (EAGAR) and the APVMA.

In June 2012, the joint Committee considered a referral from the medicines and chemicals scheduling delegates to consolidate the scheduling of all uses of tylosin in Schedule 4. The joint Committee agreed that they were unable to provide the scheduling delegates informed advice at that stage. The delegates noted that the APVMA review on macrolides was yet to be completed. The delegates therefore decided not to make a scheduling decision on this issue and referred this matter to the March 2013 joint Committee meeting for advice.

Public pre-meeting submissions

Five public submissions were received.

Two submissions supported the delegates' proposal to reschedule tylosin from Schedule 5 to Schedule 4.

One submission requested that if tylosin is included in Schedule 4, implementation time be extended to deplete the products containing tylosin currently available on the market.

One submission indicated that if tylosin is included in Schedule 4, other antibiotics with greater risk profiles for antimicrobial resistance would need to be used. The Schedule 4 listing of tylosin would also increase the cost due to the requirement of a veterinarian consultation.
One submission suggested that the delegates continue to defer the tylosin rescheduling decision until various issues, including the senate review, are resolved.

The redacted public submissions are available at http://www.tga.gov.au/industry/scheduling-submissions.htm.

Advisory Committee on Chemicals Scheduling (ACCS) advice to the delegate

The ACCS & ACMS considered the referral from the scheduling delegates to reschedule tylosin from Schedule 5 to Schedule 4 in the Standard for the Uniform Scheduling of Medicines and Poisons. The Committees advised the delegates that it was unable to make a scheduling recommendation or to provide advice at this time due to lack of provision to the Committees of all of the available data in the form of the macrolide review or an alternative acceptable process.

Delegates interim decision

The delegates have decided to defer making an interim decision on the consolidation of the scheduling of tylosin in to Schedule 4, pending receipt of further advice on the key issue of the risks of expanding antibiotic resistance associated with its use as an animal health feed additive (the current Schedule 5 and exempt uses).

Submissions on interim decision

No public submissions were received.

Delegate's consideration

The delegate considered the following in regards to this proposal:

- evaluation report (not publically available);
- scheduling proposal;
- ACCS & ACMS advice;
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[14];
- public submissions (pre-meeting); and
- other relevant information.

[14] Scheduling Policy Framework for Medicines and Chemicals <http://www.tga.gov.au/industry/scheduling-spf.htm>

Delegate final decision

The delegates have confirmed the interim decision to defer making any schedule change, pending receipt of further information. The delegates have confirmed that the reasons for deferral of a scheduling decision are in keeping with those for the interim decision.

3.3 Terminology

Scheduling proposal

The chemicals scheduling delegate and the medicines scheduling delegate (the delegates) considered a proposal to include terms, such as synthetic, analogue and derivative, to the Part 1, Introduction in order to better define these terms, their intent and purpose in the *Standard for the Uniform Scheduling of Medicines and Poisons*.

The delegates referred the proposal to the joint ACCS & ACMS for advice.

Scheduling history of synthetic cannabinoids

In July 2011, the Medicines Scheduling Delegate decided to include eight specific synthetic cannabis-like substances in Schedule 9.

In February 2012, the Medicines Scheduling Delegate decided to include another nine specific synthetic cannabis-like substances in Schedule 9.

Scheduling status of synthetic cannabinoids

There are several synthetic cannabinoids currently specifically listed in Schedule 4 (e.g. rimonabant), Schedule 8 (e.g. nabilone) and Schedule 9 (e.g. JWH-018). These entries also capture a number of other synthetic cannabinoids as derivatives in accordance with Part 1 (2) of the SUSMP.

Public pre-meeting submissions

Three public submissions were received.

A submission indicated that the current understanding of "analogue" and "derivative" encompasses "ethers, esters, and salts" and indicated that this definition may be too broad. The submission suggested that stereoisomers and salts exhibiting no substantially different pharmacological properties (both pharmacokinetic and pharmacodynamic) from the parent molecule should be considered analogues or derivatives. The submission asserted that any broadening of this definition seems to run aground against intellectual patent law.

Two submissions indicated that the recent Drug Analogue workshop proposed that a new definition of a drug analogue should replace the existing definition in the Commonwealth Criminal Code Act 1995. One of the submission noted that it was intended that this new drug analogue definition should be used in its entirety either by inclusion into or by reference from the various Australian jurisdiction drug or poisons Acts. One of these submission also suggested that the current use of the term derivative in the context of the SUSMP includes a balanced consideration of the toxicology and pharmacology of a new drug, in addition to the chemical structure. The submission suggested that any adoption of a uniform analogue definition would potentially need to be complemented by a similar consideration of the toxicology and pharmacology aspects of new drugs.

The redacted public submissions are available at: http://www.tga.gov.au/industry/scheduling-submissions.htm.

ACCS and ACMS advice to the delegate

The joint ACCS & ACMS Committee does not support the inclusion of the terms 'analogue', 'derivative' and 'synthetic' in Part 1, Interpretation, of the SUSMP.

Delegates' interim decision

The delegates considered the advice of the joint meeting of the ACCS & ACMS, advising that there is no support for including the terms 'analogue', 'derivative' and 'synthetic' in Part 1, Interpretation, of the SUSMP. The delegates noted from the discussion, that jurisdictions have been adequately served by the existing entries in Part 1. They have been able to effectively manage control over substances listed in Schedule 9, including the primary issue raised in the submission relating to interpretations involved in prosecutions. Therefore, the delegates determined that the requested changes (or clarifications) to definitions in Part 1 of the SUMSP are not warranted.

Submissions on interim decision

No submissions were received.

Delegate's consideration

The delegate considered the following in regards to this proposal:

- scheduling application;
- ACCS & ACMS advice;
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[15]; and
- other relevant information.

Delegate final decision

The delegates have confirmed the interim decision as no evidence has been received to alter the interim decision. The delegates have confirmed that the reasons for the final decision are in keeping with those for the interim decision.

Part B - Final decisions on matters not referred to an expert advisory committee

3. New chemical entities – chemicals

3.1 Cyazofamid

Scheduling proposal

The Office of Chemical Safety (OCS) evaluated the data provided in support of an application for the approval of a new active constituent namely cyazofamid. The OCS recommended that

[15] Scheduling Policy Framework for Medicines and Chemicals <http://www.tga.gov.au/industry/scheduling-spf.htm>

decoquinate be included in Schedule 5 in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).

The applicant was provided a copy of the evaluation report, but did not provide any comments.

The delegate considered this proposal and made a delegate-only decision. The Advisory Committee on Chemicals Scheduling (ACCS) was not consulted.

Toxicology

Technical Grade Active Constituent

Cyazofamid has a low acute oral (LD_{50} > 5000 mg/kg), dermal (LD_{50} > 2000 mg/kg) and inhalational (LC_{50} > 5500 mg/m^3) in rats. It was a slight irritant to rabbit eyes and a slight irritant to rabbit skin. It was not considered likely to be a skin sensitiser in guinea pigs, based on the results of a maximisation test.

In short-term dermal and subchronic oral repeat dose studies in rats and dogs, cyazofamid showed low toxicity to organs with no treatment related and toxicologically significant findings up to the highest dose tested.

In chronic oral studies in mice, rats and dogs treatment related and toxicologically significant effects were limited to an increase in histopathological changes in the ovaries (hematocysts) of mice and decreased body weight gain and increased incidence of ocular cataracts in female rats (of a similar intensity to that seen in control females) at the highest dose tested, There were no treatment related and toxicologically significant findings male mice and rats or in dogs. The above findings observed at high doses following chronic dietary exposure are not considered to require scheduling.

Cyazofamid was not carcinogenic in mice.

The uniform negative findings in a range of *in vitro* and *in vivo* studies indicate cyazofamid is not mutagenic or genotoxic.

There were no treatment related effects on reproductive or developmental parameters, with treatment related and toxicologically significant findings limited to pup toxicity (decreased body weight gain at weaning only) at the highest dose tested in a two-generation study in rats.

Neurotoxicity data were not submitted and repeat dose studies in rats did not investigate sensory reactivity to different stimuli and/or conduct a Functional Observation Battery (FOB). However, as the repeat dose toxicity data for cyazofamid indicate general low toxicity in mice, rats and dogs, and treatment related neurohistopathological lesions were not observed in chronic/carcinogenicity studies the absence of data for neurotoxicity is not considered to be of concern in this instance.

OCS has noted potential scheduling issues with regard to carcinogenicity, reproductive and developmental toxicity in their paper for the delegate's consideration.

Product

The product data was not provided with the application.

Scheduling status

Cyazofamid is not specifically scheduled and is not captured by any entry in the *Standard for the Uniform Scheduling of Medicines and Poisons*.

Scheduling history

Cyazofamid has no scheduling history.

Scheduling consideration

The delegate considered the following in regards to this application:

- the evaluation Report (not publicly available);
- section 52E of the *Therapeutic Goods Act 1989*; and
- scheduling factors for inclusion in Schedule 5[16].

Delegate's final decision

The delegate has made a delegate-only decision to include cyazofamid in Schedule 5 of the *Standards for the Uniform Scheduling of Medicines and Poisons*.

The implementation date for this decision is 1 September 2013.

The delegate decided that the relevant matters under section 52E of the *Therapeutic Goods Act 1989* include: (c) toxicity of cyazofamid.

The delegate's decision to include cyazofamid in Schedule 5 was comprised of the following reasons:

- Cyazofamid has low acute toxicity, with slight eye/skin irritancy potential. The toxicological profile of cyazofamid is consistent with Scheduling Policy Framework guidance for inclusion in Schedule 5.
- Observed effects in carcinogenicity, developmental toxicity and reproductive toxicity studies are not toxicologically significant in respect to scheduling.
- There is insufficient evidence available to consider any cut-off to exempt status.

Schedule entry

Schedule 5 – New entry

CYAZOFAMID.

3.2 Decoquinate

Scheduling proposal

The Office of Chemical Safety (OCS) evaluated the data provided in support of an application for the approval of a new active constituent namely decoquinate and registration of a new antiprotozoal product containing decoquinate at 60 g/kg (6 per cent w/w) powder. The OCS recommended that decoquinate be included in Schedule 5 in the *Standard for the Uniform Scheduling of Medicines and Poisons*.

The applicant was provided a copy of the evaluation report, but did not provide any comments. The delegate considered this proposal and made a delegate-only decision. The Advisory Committee on Chemicals Scheduling (ACCS) was not consulted.

[16] Scheduling Policy Framework for Medicines and Chemicals <http://www.tga.gov.au/industry/scheduling-spf.htm>

Toxicity

Technical Grade Active Constituent (TGAC)

Decoquinate had low acute oral toxicity in the rat (LD_{50} > 5000 mg/kg bw, no deaths) and low acute inhalational toxicity in the rat (4-hr LC_{50} > 4190 mg/m^3, nose-only). No studies on acute dermal toxicity were provided for evaluation. Decoquinate was not irritating to the eye or skin of rabbits and was not a skin sensitiser in guinea pigs.

Decoquinate did not cause any effects on reproductive parameters in a 3-generation reproduction study in rats, neither were any other toxic effects noted up to the highest dose tested (60.6 mg/kg bw/d).

In developmental studies in rats, no maternal effects were noted at the highest dose tested (300 mg/kg bw/d), however, minor developmental variations (retarded skeletal ossification) was noted at this top dose in foetal animals. In rabbits, no evidence of teratogenicity or maternal toxicity was seen at up to 300 mg/kg bw/d, the highest dose tested. However, based on equivocal results suggesting reduced mean numbers of live foetuses per litter at ≥ 100 mg/kg bw/d, and insufficient observational data to clarify the treatment-related relevance of this finding, the foetotoxicity NOEL in the rabbit developmental study was established at 60 mg/kg bw/d.

Decoquinate was negative in a range of *in vitro* mutagenicity/genotoxicity studies. Although one mouse lymphoma forward mutation assay showed equivocal results, the weight-of-evidence indicates decoquinate is not genotoxic.

Formulated product

No acute toxicity studies were provided on the product. Therefore, the potential acute oral, dermal, and inhalational toxicity, and the eye and skin irritancy and skin sensitisation potential were extrapolated from toxicity data on the active constituent and the excipients.

Based on the toxicity estimation, the product has a similar toxicity profile to the active, decoquinate, with low acute toxicity from the oral, dermal and inhalational routes expected, and not a skin irritant. The product is not expected to be a skin sensitiser. The product is a veterinary feed formulation with constituents which may cause mechanical irritation to the eyes. Additionally, one excipient present at 1 to 2 per cent of the formulation may cause health effects if chronically inhaled, however, other constituents in the formulation are expected to reduce the dusting potential.

Scheduling status

Decoquinate is not specifically scheduled.

Scheduling consideration

The delegate considered the following in regards to this application:

- the evaluation Report (not publicly available);
- section 52E of the *Therapeutic Goods Act 1989*; and
- scheduling factors for inclusion in Schedule 5[17].

[17] Scheduling Policy Framework for Medicines and Chemicals <http://www.tga.gov.au/industry/scheduling-spf.htm>

Delegate's final decision

The delegate has made a delegate-only decision to include decoquinate in Schedule 5 of the *Standards for the Uniform Scheduling of Medicines and Poisons.*

The implementation date for this decision is 1 September 2013.

The delegate decided that the relevant matters under section 52E of the *Therapeutic Goods Act 1989* include: (c) toxicity; (d) dosage, formulation and packaging; (e) potential for abuse; and (f) any other matters.

The decision to include decoquinate in Schedule 5 included the following reasons:

- The toxicological profile of decoquinate is consistent with Scheduling Policy Framework guidelines for inclusion in Schedule 5.
- The slight skin/eye irritancy is sufficient to warrant inclusion in Schedule 5, despite the overall low acute and chronic toxicity.
- There is insufficient evidence available to consider any cut-off to exempt status.

Schedule entry

Schedule 5 – New entry

DECOQUINATE.

4. New chemical entities – poisons

4.1 Megasphera elsdenii

Scheduling proposal

The Office of Chemical Safety (OCS) has evaluated the data provided in support of an application for the approval of a new microbial feed additive product, namely *Megasphaera elsdenii*, intended to aid in the transition from roughage to grain rations for beef cattle, dairy cattle and sheep to manage bloat.

The OCS recommended that *Megasphaera elsdenii* be included in Appendix B. The applicant was provided a copy of the evaluation report and agreed with the proposed schedule listing.

The delegate considered this application and made a delegate-only decision. The Advisory Committee on Chemicals Scheduling (ACCS) was not consulted.

Scheduling status

Megasphaera elsdenii is not specifically scheduled and is not captured by any entry in the *Standard for the Uniform Scheduling of Medicines and Poisons.*

Delegate's consideration

The delegate considered the following in regards to this proposal:

- the evaluation report (not publicly available);
- section 52E of the *Therapeutic Goods Act 1989*;

- scheduling factors[18]; and
- other relevant information.

Delegates' final decision

The delegate has made a final decision to include *Megasphaera elsdenii* Strain 41125 in Appendix B of the *Standard for the Uniform Scheduling of Medicines and Poisons*, with an implementation date of 1 September 2013.

The delegate considers that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (b) purpose and the extent of use and (c) toxicity.

The delegate considers that the reasons for the final decision comprise of the following:

- It has a generally low toxicity profile.
- Has no demonstrated pathogenicity or toxicity.
- The bacterium is naturally occurring in human and animal gut flora.
- The overall toxicity profile is consistent with several other direct-fed microbial substances based on bacteria commonly found in animals and humans.

Schedule entry

Appendix B Part 3 – New Entry

Substance	Date of entry	Reason for listing	Area of use
Megasphaera Elsdenii Strain 41125	Sep 2013	a	2.4

5. New chemical entities – medicines for human therapeutic use

5.1 Aclidinium Bromide

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of aclidinium bromide, a new chemical entity for a human therapeutic medicine.

Aclidinium bromide is a selective M3 muscarinic antagonist.

Aclidinium bromide is proposed for 'long-term maintenance of bronchodilator treatment to relieve symptoms in adult patients with Chronic Obstructive Pulmonary Disease (COPD).

The delegate decided to make a delegate-only decision to include aclidinium bromide in Schedule 4. The Advisory Committee on Medicines Scheduling was not consulted.

[18] Scheduling Policy Framework for Medicines and Chemicals <http://www.tga.gov.au/industry/scheduling-spf.htm>

Scheduling status

Aclidinium bromide is not specifically scheduled and is not captured by any entry in the *Standard for the Uniform Scheduling of Medicines and Poisons*.

Aclidinium bromide is not classified in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling.

- The new drug application.
- The TGA evaluation report.
- Subsection 52E(1) of the *Therapeutic Goods Act 1989*.
- The Scheduling Policy Framework scheduling factors.

Delegates' final decision

The delegate has made a final decision to amend the *Standard for the Uniform Scheduling of Medicines and Poisons* to include aclidinium bromide in Schedule 4, with an implementation date of 1 September 2013.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) risks and benefits of aclidinium bromide.

The delegate decided that the reasons for the final decision comprise of the following.

- Aclidinium bromide is a new chemical entity with no [clinical/marketing] experience in Australia.

Schedule entry

Schedule 4 – New entry

ACLIDINIUM BROMIDE.

5.2 Crizotinib

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of crizotinib, a new chemical entity for a human therapeutic medicine.

Crizotinib is an inhibitor of receptor tyrosine kinases including ALK, Hepatocyte Growth Factor Receptor (HGFR, c-Met) and Recepteur d'Origine Nantais (RON). Translocations can affect the ALK gene resulting in the expression of oncogenic fusion proteins. The formation of ALK fusion proteins results in activation and dysregulation of the gene's expression and signalling which can contribute to increased cell proliferation and survival in tumors expressing these proteins.

Crizotinib is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

The delegate has made a delegate-only decision to include crizotinib in Schedule 4. The Advisory Committee on Medicines Scheduling (ACMS) was not consulted[19].

Scheduling status

Crizotinib is not specifically scheduled and is not captured by any entry in the *Standard for the Uniform Scheduling of Medicines and Poisons*.

Crizotinib is not classified in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling.

- The new drug application.
- The TGA evaluation report.
- The advice of the Advisory Committee on Prescription Medicines.
- Subsection 52E(1) of the *Therapeutic Goods Act 1989*.
- The Scheduling Policy Framework scheduling factors.
- S60 decision and subsequent information.

Delegates' final decision

The delegate has made a final decision to amend the *Standard for the Uniform Scheduling of Medicines and Poisons* to include crizotinib in Schedule 4, with an implementation date of 1 September 2013.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) risks and benefits of crizotinib.

The delegate decided that the reasons for the final decision comprise of the following:

- Crizotinib is a new chemical entity with no marketing experience in Australia.

Schedule entry

Schedule 4 – New entry

CRIZOTINIB.

5.3 Lidocaine (Lignocaine) and Tetracaine (Amethocaine)

Scheduling proposal

The medicines scheduling delegate (the delegate) considered a proposal from the Therapeutic Goods Administration to cross-reference the International Nonproprietary Names (INNs) to the Australian Approved Names (AANs) in the index to the *Standard for the Uniform Scheduling of Medicines and Poisons*, for the Schedule entries for lignocaine and amethocaine.

[19] A new substance evaluated by the TGA is not routinely referred to a scheduling committee for advice - Scheduling Policy Framework for Medicines and Chemicals <http://www.tga.gov.au/industry/scheduling-spf.htm>

Delegate's consideration

The delegate considered the following with regard to this proposal.

- Lignocaine is the AAN and currently included in Schedules 2 and 4.
- Lignocaine is a synonym of lidocaine, the INN.
- Amethocaine is the AAN and currently included in Schedules 2 and 4.
- Amethocaine is a synonym of tetracaine, the INN
- Poisons are scheduled using their approved names, as stated under 'Reading the Schedules' in the Introduction to the SUSMP.
- The approved name for a poison that is for human therapeutic use, is the name approved for use by the TGA, as defined in Part 1, Interpretation to the SUSMP.
- The name approved for use by the TGA is the AAN.

Delegate's final decision

The delegate has made a delegate-only decision to include new entries in the Index to the *Standard for the Uniform Scheduling of Medicines and Poisons* to cross-reference lidocaine (INN) to lignocaine (AAN) and to cross-reference tetracaine (INN) to amethocaine (AAN).

The reason for the delegate's decision is to achieve clarity.

The cross-references will be included in the next consolidation of the SUSMP.

Schedule entry

SUSMP Index – New cross-reference entries

LIDOCAINE

See LIGNOCAINE

TETRACAINE

See AMETHOCAINE

5.4 Loteprednol etabonate

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of loteprednol etabonate, a new chemical entity for a human therapeutic medicine.

Loteprednol etabonate is a corticosteroid used in optometry and ophthalmology. The proposed indication is for:

- the treatment of post-operative inflammation following ocular surgery; and
- the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitis, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in oedema and inflammation.

Scheduling status

Loteprednol etabonate is not specifically scheduled and is not captured by any entry in the *Standard for the Uniform Scheduling of Medicines and Poisons.*

Loteprednol etabonate is not classified in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling.

- The new drug application.
- Subsection 52E(1) of the *Therapeutic Goods Act 1989*.
- The Scheduling Policy Framework scheduling factors.

The delegate decided to make a delegate-only decision. The Advisory Committee on Medicines Scheduling was not consulted.

Delegates' final decision

The delegate has made a final decision to amend the *Standard for the Uniform Scheduling of Medicines and Poisons* to include loteprednol etabonate in Schedule 4, with an implementation date of 1 September 2013.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) risks and benefits and (b) purpose and the extent of use.

The delegate decided that the reasons for the final decision comprise of the following.

- It is a new chemical entity with no clinical/marketing experience in Australia.
- It is a topical steroid and requires professional supervision and monitoring for initiation and continuation of use.

Schedule entry

Schedule 4 – New entry

LOTEPREDNOL ETABONATE.

5.5 Pertuzumab

Scheduling proposal

For the delegate to consider the scheduling of pertuzumab (Perjeta), a new chemical entity for a human therapeutic medicine.

Pertuzumab is a monoclonal antibody and is the first of its class in a line of agents called "HER dimerization inhibitors". By binding to HER2, it inhibits the dimerizationof HER2 with other HER receptors, which is hypothesized to result in slowed tumor growth.

It is indicated in combination with Herceptin and docetaxel for patients with HER2-positive metastatic (Stage IV) or unresectable locally recurrent breast cancer who have not received previous treatment or whose disease has relapsed after adjuvant therapy.

The delegate has made a delegate-only decision to include pertuzumab in Schedule 4. The Advisory Committee on Medicines Scheduling was not consulted.

Scheduling status

Pertuzumab is not specifically scheduled but it is captured by the Schedule 4 entry of MONOCLONAL ANTIBODIES for therapeutic use **except**:

(a) in diagnostic test kits; or

(b) when separately specified in these Schedules.

Pertuzumab is not classified in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling.

- The new drug application.
- The TGA evaluation report.
- The advice of the Advisory Committee on Prescription Medicines (ACPM).
- Subsection 52E(1) of the *Therapeutic Goods Act 1989*.
- The Scheduling Policy Framework scheduling factors for inclusion in Schedule 4.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

Delegates' final decision

The delegate has made a final decision to amend the *Standard for the Uniform Scheduling of Medicines and Poisons* to include pertuzumab in Schedule 4, with an implementation date of 1 September 2013.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) risks and benefits; (b) purpose and the extent of use; (c) toxicity and d) dosage, formulation, labelling, packaging and presentation of pertuzumab.

The delegate decided that the reasons for the final decision comprise of the following.

- Pertuzumab is a new chemical entity with no [clinical/marketing] experience in Australia.
- There is a small margin between the therapeutic and toxic dose.
- The substance is to be used for the treatment of cancer which requires expert medical diagnosis and monitoring of response to treatment.
- There is a high incidence and severity of adverse reactions.
- A risk management plan and periodic safety update reports are conditions of registration.
- The product information advises on the use of the substance.
- The Pregnancy Category is D.

Schedule entry

Schedule 4 – New entry

PERTUZUMAB.

5.6 Pralatrexate

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of pralatrexate, a new chemical entity for a human therapeutic medicine.

Pralatrexate is an antimetabolite and antineoplastic agent. It is a folate analog that inhibits folate metabolism by binding to and inhibiting the enzyme dihydrofolate reducatase with effect on the synethsis of DNA.

Pralatrexate is indicated for the treatment of adult patients with relapsed or refractoryperipheral T-cell lymphoma (nodal, extranodal and leukamic/disseminated).

The delegate decided to make a delegate-only decision to include pralatrexate in Schedule 4. The Advisory Committee on Medicines Scheduling was not consulted.

Scheduling status

Pralatrexate is not specifically scheduled and is not captured by any entry in the *Standard for the Uniform Scheduling of Medicines and Poisons*.

Pralatrexate is not classified in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling.

- The new drug application.
- The TGA evaluation report.
- The advice of the Advisory Committee on Prescription Medicines.
- Subsection 52E(1) of the *Therapeutic Goods Act 1989*.
- The Scheduling Policy Framework scheduling factors for inclusion in Schedule 4.

Delegates' final decision

The delegate has made a final decision to amend the *Standard for the Uniform Scheduling of Medicines and Poisons* to include pralatrexate in Schedule 4, with an implementation date of 1 September 2013.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) risks and benefits of pralatrexate.

The delegate decided that the reasons for the final decision comprise of the following:

- Pralatrexate is a new chemical entity with no marketing experience in Australia.

Schedule entry

Schedule 4 – New entry

PRALATREXATE.

5.7 Regorafenib

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of regorafenib, a new chemical entity for a human therapeutic medicine.

Regorafenib is an oral kinase inhibitor acting on various membrane-bound and intracellular kinases involved in cellular functions and processes, including oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment.

Regorafenib is proposed for the treatment of patients with metastatic colorectal cancer (CRC) irrespective of KRAS mutational status who have been previously treated with, or are not considered candidates for, fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.

The delegate decided to make a delegate-only decision. The Advisory Committee on Medicines Scheduling was not consulted.

Scheduling status

Regorafenib is not specifically scheduled and is not captured by any entry in the *Standard for the Uniform Scheduling of Medicines and Poisons*.

Regorafenib is not classified in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling.

- The new drug application.
- The TGA evaluation report.
- Subsection 52E(1) of the *Therapeutic Goods Act 1989*.
- The Scheduling Policy Framework scheduling factors.

Currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

Delegates' final decision

The delegate has made a final decision to amend the *Standard for the Uniform Scheduling of Medicines and Poisons* to include regorafenib in Schedule 4, with an implementation date of 1 September 2013.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) risks and benefits; (b) purpose and the extent of use, (c) toxicity and (d) dosage, packaging and presentation of regorafenib.

The delegate decided that the reasons for the final decision comprise of the following:

- Regorafenib is a new chemical entity with no clinical experience in Australia.
- There is a small margin between the therapeutic and toxic dose.
- The substance is to be used for the treatment of cancer which requires expert medical diagnosis and monitoring of response to treatment.

- There is a high incidence and severity of adverse reactions.
- A risk management plan will be a condition of registration.
- The product information will advise on the use of the substance.
- The Pregnancy Category is D.

Schedule entry

Schedule 4 – New entry

REGORAFENIB.

5.8 Ruxolitinib (Phosphate)

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of ruxolitinib phosphate, a new chemical entity for a human therapeutic medicine.

Ruxolitinib phosphate is an antineoplastic agent and tyrosine kinase inhibitor proposed for the treatment of patients with primary myelofibrosis, postpolycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.

The delegate decided to make a delegate-only decision to include ruxolitinib phosphate as ruxolitinib in Schedule 4.

The Advisory Committee on Medicines Scheduling was not consulted.

Scheduling status

Ruxolitinib phosphate or ruxolitinib are not specifically scheduled and are not captured by any entry in the *Standard for the Uniform Scheduling of Medicines and Poisons*.

Ruxolitinib is not classified in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling.

- The new drug application.
- The TGA evaluation report.
- Subsection 52E(1) of the *Therapeutic Goods Act 1989*.
- The Scheduling Policy Framework scheduling factors.

Delegates' final decision

The delegate has made a final decision to amend the *Standard for the Uniform Scheduling of Medicines and Poisons* to include ruxolitinib in Schedule 4, with an implementation date of 1 September 2013.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) risks and benefits; (b) purpose and the extent of use, (c) toxicity and (d) dosage, formulation, labelling, packaging and presentation of ruxolitinib.

The delegate decided that the reasons for the final decision comprise of the following.

- It is a new chemical entity with no clinical experience in Australia.
- There is a small margin between the therapeutic and toxic dose.
- The substance is to be used for the treatment of cancer which requires expert medical diagnosis and monitoring of response to treatment.
- There is a high incidence and severity of adverse reactions.
- A risk management plan will be a condition of registration.
- The product information will advise on the use of the substance.
- The Pregnancy Category is C.

Schedule entry

Schedule 4 – New entry

RUXOLITINIB.

5.9 Vandetanib

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of vandetanib, a new chemical entity for a human therapeutic medicine.

Vandetanib is an antineoplastic agent that inhibits the activity of tyrosine kinases including members of the epidermal growth factor receptor (EGFR) family, vascular endothelial cell growth factor (VEGF) receptors.

Vandetanib is indicated for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease.

The delegate decided to make a delegate-only decision to include vandetanib in Schedule 4. The Advisory Committee on Medicines Scheduling was not consulted.

Scheduling status

Vandetanib is not specifically scheduled and is not captured by any entry in the *Standard for the Uniform Scheduling of Medicines and Poisons*.

Vandetanib is not classified in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling:

- The new drug application.
- The TGA evaluation report.
- The advice of the Advisory Committee on Prescription Medicines.
- Subsection 52E(1) of the *Therapeutic Goods Act 1989*.
- The Scheduling Policy Framework scheduling factors.

Delegates' final decision

The delegate has made a final decision to amend the *Standard for the Uniform Scheduling of Medicines and Poisons* to include vandetanib in Schedule 4, with an implementation date of 1 September 2013.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) risks and benefits of vandetanib.

The delegate decided that the reasons for the final decision comprise of the following:

- Vandetanib is a new chemical entity with no marketing experience in Australia.
- Based on evidence provided by the sponsor in support of registration on the ARTG, the benefits of vandetanib outweigh the harms in the proposed target population.

Schedule entry

Schedule 4 – New entry

VANDETANIB.

5.10 Vismodegib

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of vismodegib, a new chemical entity for a human therapeutic medicine.

Vismodegib is an inhibitor of the Hedgehog pathway. It binds to and inhibits Smoothened, a transmembrane protein involved in Hedgehog signal transduction.

The proposed indication is for the treatment of adult patients with advanced basal cell carcinoma for whom surgery is inappropriate.

The delegate has made a delegate-only decision to include vismodegib in Schedule 4. The Advisory Committee on Medicines Scheduling was not consulted.

Scheduling status

Vismodegib is not specifically scheduled and is not captured by any entry in the *Standard for the Uniform Scheduling of Medicines and Poisons*.

Vismodegib is not classified in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling.

- The new drug application.
- The TGA evaluation report.
- The advice of the Advisory Committee on Prescription Medicines.
- Subsection 52E(1) of the *Therapeutic Goods Act 1989*.
- The Scheduling Policy Framework scheduling factors for inclusion in Schedule 4.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

Delegates' final decision

The delegate has made a final decision to include vismodegib in Schedule 4 of the *Standard for the Uniform Scheduling of Medicines and Poisons*, with an implementation date of 1 September 2013.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) risks and benefits and (f) any other matters that the Secretary considers necessary to protect public health of vismodegib.

The delegate decided that the reasons for the final decision comprise of the following:

- Vismodegib is a new chemical entity with no clinical and marketing experience in Australia.
- Vismodegib is Pregnancy Category X but its use is in a restricted population and likely to be under close supervision of appropriately specialised physicians, therefore label warnings are not considered necessary at this stage.

Schedule entry

Schedule 4 – New entry

VISMODEGIB.